Evidence-Based Versus Personalized Prostate Cancer Screening: Using Baseline Prostate-Specific Antigen Measurements to Individualize Screening

Stacy Loeb, *New York University, New York, NY*

See accompanying article on page 2705

The prostate cancer screening controversy has reached a critical turning point. There has been a 50% reduction in prostate cancer mortality in the United States, and screening is estimated to account for 45% to 70%.¹ On the other hand, screening may result in significant harms, including unnecessary biopsies with potential associated adverse effects, overdiagnosis, and resultant overtreatment.

Where should we go from here? In 2012, the US Preventive Services Task Force issued a grade D recommendation against prostate-specific antigen (PSA) screening for men of all ages.² Early data suggest that this has been associated with a reduction in the diagnosis of low-risk disease but that the proportion of high-risk cases has increased.³ Mathematical models project that abandoning screening altogether, as suggested, would eliminate overdiagnosis but also would result in a doubling of patients presenting with metastatic disease and a 13% to 20% increase in prostate cancer deaths by 2025.⁴ Thus, completely eliminating screening is not a good option, because it will also reverse the substantial progress that has been made in reducing suffering and death from advanced disease.

Most other professional societies instead recommend a shared decision-making approach, including a discussion about the pros, cons, uncertainties, and patient preferences regarding PSA-based screening.⁵⁻⁸ However, there continues to be disagreement between guidelines as to how screening should be implemented for men who opt to proceed, including the age to start and stop and the interval between tests.

The American Urological Association recommends offering PSA screening to men age 55 to 69 years, with individualized decisions in men age 40 to 55 years and screening intervals of ≥ 2 years to reduce harms.⁵ The American Cancer Society recommends offering screening beginning at age 50 years for average-risk men and in their 40s for African American men and those with a positive family history, after which it recommends using PSA levels to determine the frequency of subsequent screenings.⁷ The National Comprehensive Cancer Network and European Association of Urology recommend offering baseline PSA testing to men in their 40s and using PSA levels to determine subsequent screening intervals.^{6,8}

A major reason for this disparity between guidelines is how strictly they adhere to the protocols from randomized trials. All of the major randomized trials of PSA screening were designed in the early 1990s, initiated screening in men in their 50s, and used predefined screening intervals and a single PSA cutoff to determine

the need for prostate biopsy. These trials include the US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial that randomly assigned 76,685 men age 55 to 74 years to annual screening versus usual care and recommended a prostate biopsy for a PSA > 4 ng/mL or suspicious digital rectal examination. This study found no difference in prostate cancer mortality between the screening and usual care groups.⁹ However, these results are not surprising, given that approximately 90% of men in the usual care arm had PSA testing (more than in the screening arm).¹⁰ Therefore, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial is not informative regarding the efficacy of screening versus no screening.

The European Randomized Study of Screening for Prostate Cancer randomly assigned 162,388 men age 55 to 69 years to screening and control arms.¹¹ This study reported a significant reduction in metastatic disease and prostate cancer death with PSA screening at 2- to 4-year intervals, primarily using a PSA threshold of 3 ng/mL.

The Goteborg population-based randomized trial in Sweden randomly assigned 20,000 men to PSA screening every 2 years beginning at age 50 years and found the greatest overall reduction in prostate cancer mortality reported to date.¹² This may imply that more frequent screening in younger men accounts for the better results observed in this population compared with the rest of the European trial. Indeed, a recent study comparing men age 50 to 54 years from this trial to age-matched Swedish men from the pre-PSA era found that screening in this age group was associated with a large reduction in metastatic disease (incidence rate ratio, 0.43; 95% CI, 0.22 to 0.79) and prostate cancer death (incidence rate ratio, 0.29; 95% CI, 0.11 to 0.67).¹³

However, since the time of these randomized trials, numerous studies suggest offering screening at an even earlier age. In a large prospective US screening study, our group reported that men with a baseline PSA level in their 40s above the age-specific median of 0.7 ng/mL had a significantly higher risk of future prostate cancer diagnosis and aggressive disease.¹⁴ Conversely, among men with a baseline PSA level below the age-specific median in their 40s, only 0.3% reached the PSA threshold for biopsy of 2.5 ng/mL within the next 5 years, and only one was diagnosed with prostate cancer before age 50 years.¹⁵

Subsequent studies using stored serum samples from unscreened men in Scandinavia found that higher baseline PSA levels

predicted the long-term risk of metastatic disease and prostate cancer death.^{16,17} Using stored serum samples provided in 1981 to 1983 as part of the Copenhagen Heart Study, Orsted et al¹⁶ reported that in men younger than 45 years, the absolute 10-year risk of death from prostate cancer was 0.3%, 0.6%, 1.5%, 1.7%, 2.4%, and 9.8% for men with baseline PSA levels of 0.1 to 1.00, 1.01 to 2.00, 2.01 to 3.00, 4.01 to 10.00, and > 10 ng/mL. For men age 45 to 49 years, the corresponding 10-year risk of prostate cancer death by baseline PSA levels was 0.4%, 1.0%, 2.4%, 2.6%, 3.9%, and 16%, respectively.

A subsequent study using stored serum samples from unscreened men from Sweden showed that higher baseline PSA levels at age 45 to 49 years predicted an increased long-term risk of metastases and prostate cancer death.¹⁷ Overall, 44% of all prostate cancer deaths occurring within 25 to 30 years were in men within the highest 10th percentile of the PSA distribution (≥ 1.6 ng/mL) at age 45 to 49 years. Conversely, men with a baseline PSA level below the median of 0.68 at age 45 to 49 years had a < 0.1% risk of metastatic disease during the next 15 years.

In the article that accompanies this editorial, Preston et al¹⁸ confirm in a large US population that baseline PSA levels at a young age predict the future risk of lethal prostate cancer. Compared with men with a baseline PSA below the age-specific median, men in the > 90th percentile at age 40 to 49 and 50 to 54 years had an 8.7- and 12.6-fold increased risk, respectively, of lethal prostate cancer. Overall, 92% of lethal events occurred in men with a PSA above the median at age 40 to 49 years. By contrast, men with baseline PSA levels below the median at age 40 to 44 and 45 to 49 years had a 0.19% and 0.51% absolute risk of developing lethal prostate cancer during the next 30 years.

Overall, these studies provide consistent and compelling data that baseline PSA levels are robust predictors of future life-threatening prostate cancer. Because the baseline PSA level is a stronger predictor of future prostate cancer risk than either race or family history,¹⁴ it seems reasonable to use these values to tailor the screening protocol on the basis of the individual's level of risk. Men with PSA levels > 1 ng/mL in their 40s represent a high-risk population, for whom more frequent screening is justified. Conversely, men with a baseline PSA below the age-specific median represent a low-risk group, for whom more extended screening intervals are reasonable. It is noteworthy that the age at which screening is discontinued seems to have a larger impact on the rates of overdiagnosis than the age at which it is initiated,¹⁹ and recent studies suggest that PSA levels may also inform the optimal age to discontinue screening.^{20,21}

Although randomized trials provide the highest level of evidence, they are restricted to a specific study population and type of intervention. A one-size-fits-all approach to prostate cancer screening ignores the large variation in prostate cancer risk. This issue exemplifies the more global conflict of evidence-based versus personalized medicine, in which recommendations are tailored toward the individual.²² Must we rigidly adhere to the protocols from randomized trials providing the highest level of evidence, or should we use other high-quality data sources to refine our protocols to provide a more nuanced approach on the basis of individual characteristics? Modeling studies suggest that a risk-adapted approach to prostate cancer screening can preserve benefits with fewer harms compared with fixed screening protocols.²³

Improving the screening protocol is just one piece of the puzzle. In fact, significant progress has been made in reducing harms at each step of the path. For men with an elevated PSA, there are several new biomarkers with greater specificity that can be used to inform prostate biopsy decisions, such as the Prostate Health Index and 4K Score.⁸ For men undergoing prostate biopsy, targeted prophylaxis on the basis of rectal swab cultures has been shown to reduce the frequency of infectious complications.²⁴ New techniques of prostate biopsy using magnetic resonance imaging targeting improve the yield for clinically significant tumors while reducing the detection of insignificant prostate cancer.²⁵ Finally, there has been a large reduction in overtreatment of low-risk disease through rapidly expanding use of active surveillance.²⁶

Prostate cancer kills more than 26,000 men per year in the United States,²⁷ and there is significant morbidity in those who develop advanced disease. Only through the judicious application of screening, detection, and treatment can we further reduce morbidity and mortality from prostate cancer at a lower cost and without causing undue harm.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

REFERENCES

1. Etzioni R, Tsodikov A, Mariotto A, et al: Quantifying the role of PSA screening in the US prostate cancer mortality decline. *Cancer Causes Control* 19:175-181, 2008
2. US Preventive Services Task Force: Final Recommendation Statement. www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening
3. Banerji JS, Wolff EM, Massman JD III, et al: Prostate needle biopsy outcomes in the era of the U.S. Preventive Services Task Force recommendation against prostate specific antigen based screening. *J Urol* 195:66-73, 2016
4. Gulati R, Tsodikov A, Etzioni R, et al: Expected population impacts of discontinued prostate-specific antigen screening. *Cancer* 120:3519-3526, 2014
5. American Urological Association: Early detection of prostate cancer: American Urological Association guideline. <http://www.auanet.org/education/guidelines/prostate-cancer-detection.cfm>
6. Mottet N, Bellmunt J, Briers E, et al: EAU- ESTRO- SIOG Guidelines on Prostate Cancer. <http://uroweb.org/wp-content/uploads/EAU-Guidelines-Prostate-Cancer-2016.pdf>
7. American Cancer Society: American Cancer Society recommendations for prostate cancer early detection. <http://www.cancer.org/Cancer/ProstateCancer/MoreInformation/ProstateCancerEarlyDetection/prostate-cancer-early-detection-acs-recommendations>
8. National Comprehensive Cancer Network Guidelines: Prostate cancer early detection 2016. http://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf
9. Andriole GL, Crawford ED, Grubb RL III, et al: Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality results after 13 years of follow-up. *J Natl Cancer Inst* 104:125-132, 2012
10. Shoaq JE, Mittal S, Hu JC: Reevaluating PSA testing rates in the PLCO trial. *N Engl J Med* 374:1795-1796, 2016
11. Schröder FH, Hugosson J, Roobol MJ, et al: Screening and prostate cancer mortality: Results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet* 384:2027-2035, 2014
12. Amsrud Godtman R, Holmberg E, Lilja H, et al: Opportunistic testing versus organized prostate-specific antigen screening: Outcome after 18 years in the Göteborg randomized population-based prostate cancer screening trial. *Eur Urol* 68:354-360, 2015
13. Carlsson S, Assel M, Ulmert D, et al: Screening for prostate cancer starting at age 50-54 years. A population-based cohort study. *Eur Urol* 10.1016/j.eururo.2016.03.026 [epub ahead of print on April 12, 2016]
14. Loeb S, Roehl KA, Antenor JA, et al: Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. *Urology* 67:316-320, 2006
15. Loeb S, Nadler RB, Roehl KA, et al: Risk of prostate cancer for young men with a prostate specific antigen less than their age specific median. *J Urol* 177:1745-1748, 2007

16. Orsted DD, Nordestgaard BG, Jensen GB, et al: Prostate-specific antigen and long-term prediction of prostate cancer incidence and mortality in the general population. *Eur Urol* 61:865-874, 2012
17. Vickers AJ, Ulmert D, Sjoberg DD, et al: Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: Case-control study. *BMJ* 346:f2023, 2013
18. Preston MA, Batista JL, Wilson KM, et al: Baseline prostate-specific antigen levels in midlife predict lethal prostate cancer. *J Clin Oncol* 34:2705-2711, 2016
19. Godtman RA, Carlsson S, Holmberg E, et al: The effect of start and stop age at screening on the risk of being diagnosed with prostate cancer. *J Urol* 195: 1390-1396, 2016
20. Schaeffer EM, Carter HB, Kettermann A, et al: Prostate specific antigen testing among the elderly—when to stop? *J Urol* 181:1606-1614, 2009; discussion 1613-1614
21. Carlsson S, Assel M, Sjoberg D, et al: Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. *BMJ* 348:g2296, 2014
22. Goldberger JJ, Buxton AE: Personalized medicine vs guideline-based medicine. *JAMA* 309:2559-2560, 2013

23. Gulati R, Gore JL, Etzioni R: Comparative effectiveness of alternative prostate-specific antigen-based prostate cancer screening strategies: Model estimates of potential benefits and harms. *Ann Intern Med* 158:145-153, 2013
24. American Urological Association: AUA white paper on the prevention and treatment of the more common complications related to prostate biopsy update. <http://www.auanet.org/common/pdf/education/clinical-guidance/AUA-PNB-White-Paper.pdf>
25. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al: Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA* 313:390-397, 2015
26. Cooperberg MR, Carroll PR: Trends in management for patients with localized prostate cancer, 1990-2013. *JAMA* 314:80-82, 2015
27. American Cancer Society: Cancer facts and figures 2016. <http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf>

DOI: 10.1200/JCO.2016.68.2138; published online ahead of print at www.jco.org on June 20, 2016.

ASCO University: Your Home for the Latest Oncology Education

ASCO University, the Society's online educational home for oncology care professionals, offers lifelong learning by providing practice resources and educational opportunities for those in all oncology subspecialties. All content has gone through the ASCO review process, and oversight is provided by the ASCO University Editorial Board, thus ensuring quality, unbiased education. Content is updated weekly, so visit university.asco.org regularly for new resources.

American Society of Clinical Oncology

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Evidence-Based Versus Personalized Prostate Cancer Screening: Using Baseline Prostate-Specific Antigen Measurements to Individualize Screening

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Stacy Loeb

Honoraria: Sanofi, Bayer HealthCare Pharmaceuticals

Consulting or Advisory Role: Bayer HealthCare Pharmaceuticals

Travel, Accommodations, Expenses: Sanofi, Bayer HealthCare Pharmaceuticals

Acknowledgment

Supported by the Laura and Isaac Perlmutter NYU Cancer Center Grant P30CA016087 and the Louis Feil Charitable Lead Trust.