

CLINICAL DECISIONS

Screening for Prostate Cancer

This interactive feature addresses the diagnosis or management of a clinical case. A case vignette is followed by specific clinical options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A 55-year-old man presents to the primary care clinic for a routine health maintenance examination. He has hypertension, for which he takes a thiazide diuretic, and diabetes, which is well controlled with metformin therapy. He has no known allergies to medications. He does not smoke, and he drinks two to three beers each week. He works as an accountant and stays active by going to the gym five times a week. His blood pressure at this visit is 130/66 mm Hg. His glycated hemoglobin level, as measured recently, was 6.3%. His body-mass index (the weight in kilograms divided by the square of the height in meters) is 28. He has no symptoms of urinary frequency or difficulty voiding. He has never undergone prostate-specific antigen (PSA) testing, and at his most recent digital rectal examination, which was performed 5 years ago, no abnormalities were detected. He reports that one of his uncles recently received a diagnosis of prostate cancer at 75 years of age, and he is con-

cerned that the disease might develop in him also. He admits that he is confused by conflicting reports he has read in the newspaper about whether prostate screening is actually beneficial. He asks whether he should be screened with a digital rectal examination and a PSA test.

Which one of the following approaches would you find appropriate for this patient? Base your choice on the published literature, your own experience, recent guidelines, and other sources of information, as appropriate.

1. Recommend PSA screening.
2. Recommend against PSA screening.

To aid in your decision making, each of these approaches is defended in the following short essays by an expert in the field of prostate cancer. Given your knowledge of the patient and the points made by the experts, which approach would you choose?



Choose an option and comment on your choice at NEJM.org

OPTION 1

Recommend PSA Screening

Anthony V. D'Amico, M.D., Ph.D.

Heijnsdijk and colleagues¹ created a model using prior prostate-cancer screening data combined with an index of usefulness and outcome — utility — and now report in the *Journal* that PSA screening provides gains of up to 97 quality-adjusted life years (QALYs) or losses of up to 21 QALYs, depending on an individual utility estimate for various health states. Given that a utility estimate captures the risk associated with a decision for treatment relative to the decision

maker's risk tolerance, these data support the notion that improved patient education and a shared decision-making process could lead to gains in QALYs from PSA screening for all men.

Two previous trials^{2,3} reported reductions in prostate-cancer mortality that were associated with screening. The European Randomized Study of Screening for Prostate Cancer (ERSPC)² (the source of the data used by Heijnsdijk et al.) had a median follow-up of 11 years and reported a 21% reduction in prostate-cancer mortality; the Göteborg³ trial had median follow-up of 14 years and reported a 44% reduction in prostate-cancer mortality. Each trial used a PSA threshold

of 2.5 to 4.0 ng per milliliter (median, 3.0) as an indication for biopsy. These trials show that the number of men who would need to be screened to prevent one death from prostate cancer declines from 1410 at 9 years (ERSPC) to 1055 at 11 years (ERSPC) to 293 at 14 years (Göteborg). Although the numbers of men who would need to be screened are derived from two screening studies,^{2,3} the results suggest a greater reduction in prostate-cancer mortality with longer follow-up. This finding is relevant for young men and for men in good health even beyond the age of 70 years, given that estimates of prostate-cancer mortality began to favor screening at 7 years after randomization in both studies.^{2,3}

The U.S. Preventive Services Task Force (USPSTF) does not recommend PSA screening, on the basis of an absolute benefit in the ERSPC trial² of 1.07 fewer deaths from prostate cancer per 1000 men screened and no reduction in deaths from prostate cancer in the U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.⁴ The USPSTF decision weighed heavily the negative consequences of PSA screening, including overdiagnosis, overtreatment, and treatment complications. However, the PLCO trial⁵ was not informative, because 44% of men underwent PSA screening before randomization and 85% of men in both randomized arms attended at least one PSA screening⁵ — factors that markedly reduced power to observe a difference in deaths from prostate cancer. The USPSTF decision also failed to consider the increase in the number of lives saved with longer follow-up, as reflected in the decreased number of men who would need to be screened to prevent one death from prostate cancer. Although the ERSPC trial did not show an overall mortality benefit from screening, additional years of follow-up may show such a benefit.

For the 55-year-old man described in the vignette, we would expect results similar to those in the Göteborg trial,³ in which the median age was 56 years: screening resulted in nearly a halving of prostate-cancer mortality at 14 years. Therefore, assuming that the digital rectal examination is normal, that you have counseled the patient regarding the risks of biopsy, and that he agrees to a biopsy should his PSA level be above 3.0 ng per milliliter, I recommend that the patient undergo PSA screening.

If low-risk prostate cancer is diagnosed (PSA

level <10 ng per milliliter, Gleason score ≤ 6 , and stage T1c or T2a disease), the patient should be counseled that since a survival benefit has not been observed after a median follow-up of 10 years in the Prostate Cancer Intervention versus Observation Trial (PIVOT),⁶ active surveillance could be considered. If intermediate or high-risk prostate cancer is diagnosed (PSA level ≥ 10 , Gleason score ≥ 7 , or disease stage $\geq T2b$), given the potential survival benefit with treatment versus observation in PIVOT,⁶ the patient should be counseled regarding the risks of treatment and the potential survival advantage before deciding on treatment.

By adopting this shared decision-making approach, with prior discussion of both screening and treatment options, we may enable all men to gain QALYs from PSA screening. By providing risk-group–based information on survival benefit with treatment versus observation, practitioners can help patients make a fully informed screening decision.

Disclosure forms provided by the author are available at NEJM.org.

From Brigham and Women's Hospital and Dana–Farber Cancer Institute — both in Boston.

OPTION 2

Recommend against PSA Screening

Matthew R. Smith, M.D., Ph.D.

To screen or not to screen for prostate cancer? The USPSTF recommends against PSA-based screening for prostate cancer, concluding that there is moderate or high certainty that PSA screening has no net benefit.⁷ The recommendation of the task force was based primarily on the results of two large, randomized, controlled trials of prostate cancer screening, the PLCO Cancer Screening Trial⁴ conducted in the United States and ERSPC conducted in Europe.² The PLCO trial showed no significant difference in prostate-cancer mortality or all-cause mortality between patients who underwent annual screening and those who received usual care. The ERSPC found a small reduction in prostate-cancer mortality but no significant difference in all-cause mortality. Furthermore, screening is associated with a variety of harms, including unnecessary

biopsies, overdiagnosis, overtreatment, and treatment-related complications such as urinary incontinence, erectile dysfunction, and bowel dysfunction. Heijnsdijk et al.¹ report in the *Journal* that harms reduced the unadjusted life-year benefits of screening in ERSPC by 23% — although this estimate is very dependent on the utility estimates assigned to various health states.

Criticisms of the USPSTF recommendation have focused on flaws in the PLCO trial and ERSPC.⁸ The PLCO trial had a high rate of contamination by PSA testing before study entry and nonprotocol PSA testing in the control group. The median follow-up period in both studies was approximately 11 years — a relatively short interval for this indolent cancer. Nonetheless, the estimated benefit of PSA screening and early treatment is between 0 and 1 prostate-cancer death prevented for every 1000 men screened, with no decrease in all-cause mortality in the first decade of screening. Only time will tell whether longer follow-up will accumulate greater benefits of screening.

Proponents of PSA screening have also criticized the USPSTF for failing to consider the evidence that treatment for clinically localized prostate cancer reduces mortality. There is little evidence, however, that early treatment reduces mortality among men with prostate cancer identified by screening. Two randomized trials compared the strategies of radical prostatectomy and observation in the era before widespread PSA testing. A small study conducted by the Veterans Administration Cooperative Urological Research Group showed no significant difference in overall survival after more than 20 years of follow-up.⁹ The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) did show an improvement in prostate-cancer-specific and overall survival with screening as compared with observation.¹⁰ However, these findings cannot be generalized to men with low-risk prostate cancers identified by PSA screening, because prostate cancer was diagnosed by means of screening in only 5.2% of men in SPCG-4. In the more contemporary PIVOT, involving men with clinically localized cancers that were diagnosed in

tomy did not reduce all-cause or prostate-cancer mortality through at least 12 years of follow-up.⁶ The effects of treatment on all-cause and prostate-cancer mortality did not differ significantly according to age, race, coexisting conditions, or histologic features of the tumor.

The 55-year-old man in this clinical vignette has a lifetime risk of death from prostate cancer of approximately 3%. With screening, he is more likely to have early complications related to unnecessary biopsies, overdiagnosis, or overtreatment than to prevent a distant death from prostate cancer. The available evidence is insufficient for clinicians to recommend routine PSA screening for men at average risk for prostate cancer. Some men will continue to choose PSA testing, but screening should be a shared decision that considers individual views about both the established harms and possible latent benefits.

Disclosure forms provided by the author are available at NEJM.org.

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