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REFERENCES

1. Gawande A. Overkill: an avalanche of unnecessary medical care is harming patients physically and financially—what can we do about it? *The New Yorker*. http://www.newyorker.com/magazine/2015/05/11/overkill-atul-gawande. Accessed October 22, 2015.

2. Hendel RC, Patel MR, Allen JM, et al. Appropriate use of cardiovascular technology: 2013 ACCF appropriate use criteria methodology update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force. *J Am Coll Cardiol*. 2013;61(12):1305-1317.

3. The Dartmouth Atlas of Healthcare website. http://www.dartmouthatlas.org. Accessed October 22, 2015.

4. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA Clinical Practice Guideline Recommendation Classification System [published online September 3, 2015]. *J Am Coll Cardiol*. doi:10.1016/j.jacc.2015.09.001.

5. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA*. 2009;301(8):831-841.

6. IHI Triple Aim Initiative. Institute for Healthcare Improvement website. http://www.ihi.org/engage/initiatives/tripleaim/Pages/default.aspx. Accessed October 22, 2015.

7. Institute of Medicine. The Learning Healthcare System in America. National Academies website. https://iom.nationalacademies.org/Activities/Quality/LearningHealthCare.aspx. Accessed October 22, 2015.

8. Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey. *J Am Coll Cardiol*. 2014;64(13):1373-1384.

9. Patel MR, Spertus JA, Brindis RG, et al. ACCF proposed method for evaluating the appropriateness of cardiovascular imaging. *J Am Coll Cardiol*. 2005;46(8):1606-1613.

10. Patel MR, Wolk MJ, Allen JM, Dehmer GJ, Brindis RG. The privilege of self-regulation: the role of appropriate use criteria. *J Am Coll Cardiol*. 2011;57(14):1557-1559.

11. Fogel RI, Epstein AE, Mark Estes NA III, et al. The disconnect between the guidelines, the appropriate use criteria, and reimbursement coverage decisions. *J Am Coll Cardiol*. 2014;63(1):12-14.

12. Desai NR, Bradley SM, Parzynski CS, et al. Appropriate use criteria for coronary revascularization and trends in utilization, patient selection, and appropriateness of percutaneous coronary intervention [published online November 9, 2015]. *JAMA*. doi:10.1001/jama.2015.13764.

13. Masoudi FA. Reflections on performance measurement in cardiovascular disease. *Circ Cardiovasc Qual Outcomes*. 2011;4(1):2-4.

14. James S, Rao SV, Granger CB. Registry-based randomized clinical trials—a new clinical trial paradigm. *Nat Rev Cardiol*. 2015;12(5):312-316.

15. PCORnet, the National Patient-Centered Clinical Research Network website. http://www.pcornet.org. Accessed October 22, 2015.

The Pendulum of Prostate Cancer Screening

David F. Penson, MD, MPH

In May 2012, the US Preventive Services Task Force (USPSTF) recommended against prostate-specific antigen (PSA)-based screening for prostate cancer, giving it a grade D and concluding, "there is moderate certainty that the benefits of PSA-based screening from prostate cancer do not outweigh the harms."[1] Rather than put an end to this controversy over screening, this recommendation further fueled a contentious ongoing debate.

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Two large randomized clinical trials studying the effectiveness of prostate cancer screening have been completed to date.[2,3] In the United States, the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) study failed to show a survival benefit for prostate cancer screening. However, participants in the control group of PLCO underwent an average of 2.7 PSA tests and 74% had at least 1 PSA test during the study period,[4] leading many to suggest that this was not a valid comparison of screening with no screening. A second large study, the European Randomized Study of Screening for Prostate Cancer (ERSPC), with less contamination of the control group, showed a benefit to PSA screening, although the effect size was relatively small and the risk of overdiagnosis and overtreatment associated with screening remained substantive.

Proponents of the USPSTF recommendation against screening primarily rely on these 2 studies to support their position. Conversely, supporters of PSA screening cite the separately published Goteborg component of the ERSPC trial that showed a considerably greater benefit to PSA screening.[5] They maintain that the principal harm of screening, overtreatment, is declining in the United States, as more patients with low-risk prostate cancer (generally defined disease in which the patient has a PSA level <10 ng/mL, a normal digital rectal examination finding [clinical stage T1c], and pathologically well-differentiated disease [Gleason sum ≤6])[6] elect active surveillance—a therapeutic strategy in which serial PSA measurements and follow-up prostate biopsies are obtained and intervention is undertaken only if there is evidence of progression.[7] While both sides remain entrenched in the absolute belief that they are right, patients and physicians are caught in the middle, uncertain about whether the benefits of PSA screening outweigh the harms.

Two studies in this issue of *JAMA*, by Sammon and colleagues[8] and by Jemal and colleagues,[9] document that the

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2012 USPSTF recommendation has been temporally associated with a decline in PSA screening and prostate cancer incidence. Both reports use the National Health Interview Survey to demonstrate that self-reported PSA screening rates declined significantly from 2010 to 2013. Based on a study population of 20 757 men 50 years and older, Sammon et al[8] report that the prevalence of self-reported PSA testing was 35% in 2000 and 2005, was 36% in 2010, and declined to 31% in 2013. Jemal and colleagues[9] also use data from the Surveillance, Epidemiology, and End Results (SEER) registries to document a decline in prostate cancer incidence among men 50 years and older from 2008 (540.8 cases/100 000 men) to 2012 (416.2 cases/100 000 men), with the largest decrease occurring between 2011 (498 cases/100 000 men) and 2012, coinciding with the release of the USPSTF recommendation. The authors also estimate the absolute reduction in new prostate cancer cases in the United States by combining data from the SEER program and the National Program of Cancer Registries, resulting in coverage of 99.2% of the US population, and suggest that the number of men diagnosed with prostate cancer in the United States decreased from 213 562 in 2011 to 180 043 in 2012, representing an estimated absolute reduction of 33 519 fewer cases nationwide. Although it is impossible to conclude that this number of additional cases would have been diagnosed had PSA screening utilization remained stable, it is likely that the vast majority of them would have been detected had screening rates remained unchanged.

There are certainly pros and cons associated with this decline in prostate cancer incidence. The ERSPC results can be used to estimate an upper bound of the potential harms associated with this decline in incident cases. The ERSPC investigators estimated that after 13 years follow-up, 27 additional prostate cancer cases needed to be detected (NND) in the screening group to prevent 1 prostate cancer death.[3] Given that Jemal et al[9] estimated that 33 519 fewer cases were detected in 2012, a similar extrapolation as used in the ERSPC would suggest that approximately 1241 (33 519/27) more men will die of prostate cancer. This estimate is based on numerous assumptions, however, such as that the prostate cancers detected by routine screening are identical to the cancers detected in the ERSPC trial and that the underlying prostate cancer risk is comparable between the ERSPC population and the general population in the United States.

Some assumptions may not be completely valid, but this estimate likely still provides a rough approximation of the number of prostate cancer deaths that will be related to this 1-year decline in PSA screening rates and the related decrease in disease incidence. This estimate may even be somewhat conservative because other investigators have suggested that the NND associated with the ERSPC will decline further as the trial accrues longer follow-up. Gulati et al[10] estimated that the NND associated with the ERSPC trial will decrease to 9 cases after 25 years of follow-up, and Heijnsdijk et al[11] estimated that, with lifetime follow-up and quality-of-life adjustment, the NND from ERSPC could decrease to as low as 5 cases, which would result in a further increase in the estimated number of prostate cancer deaths.

Although it is essential to acknowledge that these projections are rough approximations, they still indicate the potential for some degree of harm in the form of excess mortality due to prostate cancer associated with the decline in PSA screening that has occurred following the USPSTF recommendation. A formidable challenge in determining the effectiveness of PSA screening arises because prostate cancer–related mortality, when it occurs, happens long after diagnosis. Draisma et al[12] estimated the lead time associated with PSA screening to be as long as 5 to 7 years, with mortality still occurring many years after that. Therefore, the increase in prostate cancer mortality rates associated with the 2012 decrease in PSA screening is unlikely to be detected until 2022 or later. The most relevant outcome metric to evaluate the effectiveness of cancer screening tests is mortality, not incidence. However, the relatively indolent nature of many prostate cancers and the reality that many men die with, not of, prostate cancer make the determination of the risk-benefit ratio for PSA screening difficult to establish.

There are also benefits associated with reduced PSA screening. There is little doubt that if screening rates had remained stable, many men who would have been diagnosed with prostate cancer would have had clinically indolent disease and would have been exposed to the considerable adverse effects of surgery or radiation, such as sexual, urinary, or bowel problems, with little or no survival benefit. Acknowledging this, there is increasing evidence that active surveillance is becoming a preferred management strategy for men with low-risk disease.[7] This approach effectively minimizes overtreatment while reserving intensive therapy for patients who will likely obtain the greatest benefit, those with higher-risk disease. Those who oppose routine PSA screening are correct in pointing out that overdiagnosis and overtreatment will still occur, even with increased utilization of active surveillance. However, patterns of care in prostate cancer treatment are clearly changing, potentially altering the harm-benefit equation for prostate cancer screening.

Acknowledging the difference in opinions on PSA screening, it is time to put aside the rhetoric and try to develop better ways to screen for this common malignancy. The PSA test is certainly imperfect, but perhaps, as suggested by Barry and Hayes[13] in their article in this issue of *JAMA*, the PSA test can be deployed more effectively (or strategically), maximizing benefit while minimizing harm. For example, the American Urological Association's Early Detection of Prostate Cancer guidelines[14] suggest that a routine screening interval of 2 years or longer may be preferred over annual screening. This recommendation was based on a modeling study that used data from the control group of the Prostate Cancer Prevention Trial to show that using a higher PSA threshold in older men and extending the screening interval was associated with reduced harms related to screening while preserving the number of lives saved.[15]

Furthermore, it may be possible to individualize PSA screening strategies by quantifying baseline risk for high-risk prostate cancer. For example, in a study involving 21 277 men from Malmo, Sweden, Vickers and colleagues[16] found that a single PSA measurement of greater than 1.6 μg/L

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in men aged 45 to 49 years was associated with a 5.14% greater risk of dying of prostate cancer within 25 years of testing. Perhaps the frequency of further PSA screening should be based on a single initial measurement at a relatively younger age. Another potential method for identifying men at increased risk for high-risk prostate cancer is to use widely available nomograms, such as the Prostate Cancer Prevention Trial risk calculator.[17] This approach could aid in assessing the patient's pretest probability of high-risk prostate cancer and help individualize further PSA screening schedules. All of these possible solutions are based on simple Bayesian principles to arrive at potentially better screening strategies.

In summary, there is reason to be concerned about the decline in prostate cancer screening and prostate cancer incidence reported by Sammon et al[8] and Jemal et al.[9] Certainly, physicians have been overly aggressive in their approach to prostate cancer screening and treatment during the past 2 decades, but the pendulum may be swinging back the other way. It is time to accept that prostate cancer screening is not an "all-or-none" proposition and to accelerate development of personalized screening strategies that are tailored to a man's individual risk and preferences. By doing this, it should be possible to reach some consensus around this vexing problem and ultimately help men by stopping the swinging pendulum somewhere in the middle.

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REFERENCES

1. Moyer VA; US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157(2):120-134.

2. Andriole GL, Crawford ED, Grubb RL III, et al; PLCO Project Team. 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*. 2012;104(2):125-132.

3. Schröder FH, Hugosson J, Roobol MJ, et al; ERSPC Investigators. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet*. 2014;384(9959):2027-2035.

4. Pinsky PF, Blacka A, Kramer BS, Miller A, Prorok PC, Berg C. Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. *Clin Trials*. 2010;7(4):303-311.

5. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol*. 2010;11(8):725-732.

6. Mohler JL, Kantoff PW, Armstrong AJ, et al; National Comprehensive Cancer Network. Prostate cancer, version 2.2014. *J Natl Compr Canc Netw*. 2014;12(5):686-718.

7. Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990-2013. *JAMA*. 2015;314(1):80-82.

8. Sammon JD, Abdollah F, Choueiri TK, et al. Prostate-specific antigen screening after 2012 US Preventive Services Task Force recommendations. *JAMA*. doi:10.1001/jama.2015.7273.

9. Jemal A, Fedewa SA, Ma J, et al. Prostate cancer incidence and PSA testing patterns in relation to USPSTF screening recommendations. *JAMA*. doi:10.1001/jama.2015.14905.

10. Gulati R, Mariotto AB, Chen S, Gore JL, Etzioni R. Long-term projections of the harm-benefit trade-off in prostate cancer screening are more favorable than previous short-term estimates. *J Clin Epidemiol*. 2011;64(12):1412-1417.

11. Heijnsdijk EAM, Wever EM, Auvinen A, et al. Quality-of-life effects of prostate-specific antigen screening. *N Engl J Med*. 2012;367(7):595-605.

12. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst*. 2009;101(6):374-383.

13. Barry MJ, Hayes JH. Evaluating an elevated screening PSA test. *JAMA*. doi:10.1001/jama.2015.12614.

14. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. *J Urol*. 2013;190(2):419-426.

15. 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*. 2013;158(3):145-153.

16. 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*. 2013;346:f2023.

17. Ankerst DP, Boeck A, Freedland SJ, et al. Evaluating the PCPT risk calculator in ten international biopsy cohorts: results from the Prostate Biopsy Collaborative Group. *World J Urol*. 2012;30(2):181-187.

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