

Lack of persuasive data continues to plague PSA testing

1 **Anticipated results from a duo of randomized trials led to more am-** 51
 2 **biguity than clarity. Trial investigators, along with outside experts,** 52
 3 **discuss the future of the prostate cancer test.** 53
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6 **BY RONALD PIANA** 56
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9 Is the era of PSA screening coming to an 59
 10 end? Proponents say the test saves lives, 60
 11 but a growing number of critics contend 61
 12 that widespread screening does more 62
 13 harm than good. The ongoing controversy 63
 14 over the clinical value of PSA screening 64
 15 has long been perpetuated by a lack of 65
 16 persuasive data, leaving doctors and their 66
 17 patients with difficult conversations and a 67
 18 host of perplexing decisions. 68

19 The much-anticipated results from 69
 20 two large randomized trials—U.S.-based 70
 21 PLCO trial and the Europe-based ERSPC 71
 22 study—fostered more ambiguity than 72
 23 clarity (*New Engl J Med* 360:1310-1328 73
 24 2009). Experts extrapolated what these 74
 25 study results mean in routine practice for 75
 26 *Oncology News International*. 76

27 **Risk reduction vs quality of life** 77

28 “We’re not left knowing much more than 78
 29 we did before the studies,” said Peter Bach, 79
 30 MD, an associate attending physician at 80
 31 New York’s Memorial Sloan-Kettering 81
 32 Cancer Center. “The U.S. study appears 82
 33 to be negative, but there’s a meaning- 83
 34 ful amount of contamination and there 84
 35 may be insufficient follow-up. However, 85
 36 the European study looks like it’s posi- 86
 37 tive to the tune of a 20% reduction in 87
 38 mortality.” 88
 39 89

40 But in order to put the PSA issue in a 90
 41 population-based health perspective, “we 91
 42 need to fully understand the trade-off 92
 43 between mortality risk reduction and the 93
 44 obvious detriment to quality of life in men 94
 45 who were treated earlier than necessary or 95
 46 to those who shouldn’t have been treated 96
 47 at all,” Dr. Bach added. 97

48 “We need better quality-of-life in- 98
 49 formation in order to figure out how to 99
 50 balance the trade-off between potential 100

benefits and overdiagnosis. On a popula- 59
 tion health basis, we can’t go by mortal- 60
 ity statistics and say that serious harms 61
 associated with too-early or unnecessary 62
 treatments don’t matter,” he said. 63

“If the European study was also nega- 64
 tive, then we’d have a different problem. 65
 We’d say, ‘OK, we now realize that PSA 66
 doesn’t work, but how do we get the PSA 67
 genie back in the bottle?’” Dr. Bach said. 68

Dr. Bach stressed that the European 69
 study’s long lag time to benefit and mul- 70
 ticountry design raise certain design 71
 questions, but if the reported 20% mor- 72
 tality reduction is proven valid, then PSA 73
 screening confers about the same survival 74
 advantage as does mammography. 75

“If this were a painless pill, then PSA 76
 screening is a no-brainer. But since we 77
 can’t accurately describe the clinical trade- 78
 offs well enough for individual men to 79
 make an informed decision, we certainly 80
 can’t cast a broader PSA screening policy,” 81
 Dr. Bach said. 82

83 **Is more focus on high risk needed?** 84

85 Susceptibility to developing prostate 85
 86 cancer has a highly heritable compo- 86
 87 nent—men who have a first-degree rela- 87
 88 tive with the disease are at much higher 88
 89 risk than those who do not have a family 89
 90 history. True believers in PSA will cite 90
 the European study’s report that lives 91
 may be saved by screening and the true 92
 nonbelievers will cite the U.S. study’s lack 93
 of survival benefit, said Derek Raghavan, 94
 MD, PhD. 95

“However, right now we should discuss 96
 and advise our patients without being 97
 zealots and confusing them. Without 98
 good data, I continue to be extra careful 99
 with my patients who have a family history 100

1 (especially those with deaths from prostate cancer) and African Americans, who reportedly have a worse survival,” said Dr. Raghavan, who is chair of The Cleveland Clinic’s Taussig Cancer Institute.

2 Dr. Raghavan noted that a crucial piece of the prostate cancer conundrum is the cancer itself. “There are two different types of prostate cancer, one that progresses very slowly and is less dangerous, and one that can progress quickly, causing widespread and potentially lethal disease,” he said. “The vexing problem is that it is very difficult to differentiate the indolent from the aggressive types.”

17 **PLCO investigators weigh in**

18 A *New England Journal of Medicine* poll taken after the release of the two studies illustrates the quandary surrounding the efficacy of PSA screening. Asked whether routine PSA screening was justified, 23 44% said yes, while 54% said no (1134 respondents).

25 **Edward P. Gelmann, MD**, one of the PLCO authors, told *Oncology News International* that despite the indecisive results from both trials, “men continue to want to know if they have prostate cancer. Our biggest challenge is stratifying the various levels of risk that men have so we can better identify who should be screened.”

33 “The results of the two studies tell us that PSA testing is actually too sensitive, which presents the problem of potential overdiagnosis,” said Dr. Gelmann, who is the Clyde and Helen Wu professor of medicine at New York’s Herbert Irving Comprehensive Cancer Center, Columbia University.

41 Proponents of PSA make the argument that since the introduction of screening two decades ago, rates of metastatic prostate cancer have dropped significantly. To that, Dr. Gelmann replied, “Most of the leading epidemiologists who have looked at this issue conclude that PSA screening, which started substantially in the late 1980s, began too late to affect the drop in mortality that we saw in the

mid-1990s.”

In other words, Dr. Gelmann explained, the temporal relationship between PSA screening and the drop-off of late-stage prostate cancer diagnosis “is more likely due to changes in management, changes in awareness, and improved treatments than to PSA screening.”

Dr. Gelmann also pointed out that many mainstream articles have stated that the two randomized trials reported conflicting survival results. If anything, the two trials suffer from being reported too soon. “If you draw a line at the European study at 10 years, the results are the same as the US study,” he said.

PLCO study coauthor **E. David Crawford, MD**, head of urologic oncology at the University of Colorado in Denver, told *Oncology News International* that the primary reason the PLCO study found little difference in survival between the screened and control groups is “because screening simply does not work.” He emphasized that men need to be informed about the risks and potential harms involved in PSA screening. “But it is very important in all these discussions to separate diagnosis from treatment,” he added.

The bottom line: “Nearly 30,000 men in the United States die of prostate cancer each year. We need to look for better detection devices and ways to determine the aggressiveness of the cancer,” Dr. Crawford said.

87 **PSA still vital**

88 Although both trials found insufficient evidence to support or refute the efficacy of prostate screening, many doctors who treat prostate cancer are adamant about the life-saving value of the test.

93 “I’ve lived through the pre-PSA era, and I think it would be a mistake to abandon PSA screening,” said **Judd Moul, MD**, director of the Duke University Prostate Center.

98 Although PSA is an extremely sensitive indicator, the test itself is not cancer-specific. A high reading must be followed by

1	a biopsy, which, if positive, opens another	51
2	door in the variable and confusing world	52
3	of prostate cancer screening.	53
4	Dr. Moul stressed that we need to prac-	54
5	tice better risk stratification in younger	55
6	men, beginning baseline testing at age	56
7	40. "If they have a PSA of one, then we	57
8	revisit the test at age 45. And in older	58
9	populations, if they present with prostate	59
10	cancer, we should also do risk stratifica-	60
11	tion, because not all will need aggressive	61
12	treatment."	62
13	Dr. Mould voiced concern that a mis-	63
14	guided backlash against PSA screening	64
15	might deter men from having the test. "I	65
16	don't want to go back to the days when	66
17	I had patients all over the ward dying	67
18	with excruciating bony metastases. We	68
19	shouldn't put our heads in the sand and	69
20	stop utilizing this test that over the years	70
21	has saved countless thousands of lives,"	71
22	Dr. Moul said. ■	72
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