The United States Preventive Services Task Force Recommendation against Prostate-Specific Antigen Screening—Point

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Screening is one of the cornerstones of preventive medicine. The purpose of screening is to identify preclinical and asymptomatic cases of disease in a population at risk—as opposed to making a diagnosis based on a patient’s presentation with symptoms and disease. The assumption is treatment in the early stages of disease is often less aggressive, more effective than in the later stages of disease, and has the potential to reduce morbidity and mortality. Population screening, providing the appropriate prerequisites are in place, inclusive that the potential benefits outweigh the harms (1), is critical to the success of preventive medicine. Therefore, early detection through screening, a subject of increasing controversy of late, can be a double-edged sword, helping in some instances and being of harm in others.

Perhaps, because of the dramatic two-fold increase in the lifetime risk of a diagnosis of prostate cancer owing to widespread prostate-specific antigen (PSA) screening of asymptomatic men for prostate cancer (2) and subsequent treatment of many, possibly unnecessarily, with attendant morbidities and mortalities, no other disease presently better exemplifies the controversy of screening.

In the best interest of men’s health, the all too slowly increasing crescendo of the controversy and debate about PSA screening came in October 2011, when the U.S. Preventive Services Task Force (USPSTF) recommended the PSA test not be used to screen asymptomatic men younger than 75 years of age for prostate cancer (3). The principal findings of the USPSTF evidence-based review were that PSA screening does not save lives and does more harm than good (3).

From my perspective as the discoverer of PSA in the normal (in 1970; refs. 4, 5) and the benign and malignant (in 1972; ref. 6) human prostate, which was subsequently purified and characterized in 1979 (7), the controversy and debate of PSA screening were predictable from the onset and should have never in all actuality occurred, nor should have the tragedy of the resulting overdiagnosis and overtreatment in excess of a million men in the United States (8).

The “science” of the PSA test was extrapolated beyond its capabilities to serve as a harbinger for the recurrence of prostate cancer for the purpose of screening and the medical community was too quick to biopsy and treat.

With the foregoing premise, it is the author’s opinion that the outcome of the studies on which the USPSTF evidence-based review and recommendation have been made will become quite understandable and acceptable by looking back at the “science” on which PSA screening for prostate cancer has been based.

In looking back, one has to appreciate that PSA is a normal component of the prostate (4, 5). Present in the normal, benign, and malignant prostate (6), PSA is therefore, not cancer-specific, but prostate-specific. On the basis of the specificity of PSA for the prostate, in 1986 (9), the U.S. Food and Drug Administration (FDA) approved the subsequently developed PSA test (10)—a means by which to quantify blood (serum) levels of PSA, for monitoring disease status in patients with prostate cancer as a harbinger for the recurrence of prostate cancer following treatment. Note, it was not “cancer” that was and is detected, but PSA-specific for the prostate.

Enthusiastic over the prospect of a blood test for the presence or absence of prostate cancer, albeit not cancer-specific, led many, due to the uncertainty of a digital rectal examination (DRE) for a presumptive diagnosis of prostate cancer, to use the PSA test for the screening of prostate cancer even without FDA approval. Buoyed significantly by the early landmark study of Stamey and colleagues (11), wherein the level of PSA was reported proportional to increasing palpable stages and volume of prostate cancer followed by clever marketing of PSA test manufacturers; the media, through high-profile political, entertainment, and professional sports figures, and well-intended, but ill-informed urologists, screening proliferated to a “fervor which would not disgrace a medieval inquisition” (12).

In reference to the report by Stamey and colleagues (11), in retrospect, reveals that the relationship between PSA and cancer was only approximately 50%, with a reasonable amount of PSA attributable to the benign component of the prostate. Stamey, in 2002 (13), 15 years later, recanted his position indicating that it was predominantly benign prostatic hypertrophy (BPH) that was associated with the increased PSA and stated “We originally thought we were doing the right thing….” (14) in reference to conducting radical prostatectomies.
When the FDA approved the PSA test in 1994 (15), as an early test for the detection of prostate cancer in men older than 50 years of age when combined with a DRE, their evaluation was not based on a rigorous study of the specificity and sensitivity of the test. This is particularly puzzling given the prior knowledge that PSA was not cancer-specific (6) and therefore could not be diagnostic of cancer. Furthermore, the FDA never looked at the benefits and risks of the test.

In retrospect of FDA approval of the PSA test, it is noteworthy, that in addition to this author, earlier investigators associated with the development of the test were knowledgeable in their studies in the early 1980s that PSA was not cancer-specific (16), wherein an elevation could be reflective of prostatitis, BPH, and/or other confounding factors; and these same investigators thought PSA inappropriate for screening because of poor specificity (17). Albeit supportive of my initial assessment of PSA, this is paradoxical, for if PSA had poor specificity, then, it has the same poor specificity now! Perhaps, the failure of others to own up to their observations in promulgating the use of PSA screening becomes less of a paradox given a recent quote from Gilbert Welch commenting on screening "We were afraid to say exactly what we thought for fear of seeming too crazy. It was easy to get financing to study the benefits of screening, but a study that looked at harms was too far out of the culture" (18). The ability of the FDA-approved PSA test to identify men at risk for prostate cancer is slightly better than the flip of a coin. Prostate cancer is an age-related disease (19). A PSA-promoted biopsy may or may not, related to the age of the individual, find cancer, which according to some, may be related to "how hard it (i.e., the cancer) is looked for" (20). With approximately 45% to 80% of men screened between the ages of 50 and 75 years old possessing latent (histologic) asymptomatic cancer (19), cancer may very well be found. However, we cannot determine whether it is an indolent, clinically insignificant cancer requiring no treatment, or an aggressive cancer that may require treatment, lest it metastasizes.

Combine the absence of cancer specificity of the PSA test, the age relatedness of prostate cancer, and the inability of the PSA test to distinguish between an indolent and aggressive cancer with the observation that there is no single or absolute level of PSA definitive for prostate cancer (21) and what do you have? The result is you have a test, mindful its intent is for screening, for which I ask: "What if anything does it tell us relative to the purpose of screening for prostate cancer, which is to identify preclinical and asymptomatic cases?" To be clear that there is no misunderstanding, therefore, no level of PSA is maximally sensitive and specific, which allows for both false-positive and false-negative results within the heretofore threshold or range of PSA >4 ng/mL, but rather a continuum of cancer risk at all values of PSA.

For completeness, several PSA-related concepts have been brought forth in an endeavor to rectify not only the absence of cancer specificity but other confounding factors of PSA screening, notably, the reduction of unnecessary biopsies. These, for which the initial are referred to as "first generation" to distinguish them from recent "second generation" PSA-related concepts, as considered in detail elsewhere (22, 23) are inadequate. However, some "second generation" PSA-related concepts (23), inclusive of select precursors of PSA, or isoforms of free PSA have shown limited but interesting results (24).

Beyond the scope of this Editorial, a comprehensive consideration of PSA testing across the spectrum of prostate cancer will be found in a recent overview (23).

Given that (i) PSA is not cancer-specific; (ii) prostate cancer is an age-related disease; (iii) the PSA test cannot distinguish an indolent from an aggressive cancer; and (iv) there is no level of PSA diagnostic for prostate cancer, therein lie the fundamental cruxes for the inability of the use of the PSA test for screening of asymptomatic men for prostate cancer to do what it has been purported to do and in the process result in the overdiagnosis and overtreatment in excess of a million men in the United States (8). With the foregoing having been brought forth for over 17 years (as we have seen the PSA test has been used for screening prior to FDA approval in 1994) until the USPSTF findings and recommendation on October 7, 2011 (3), that use of the PSA test for screening of asymptomatic men for prostate cancer causes more harm than good and is a liability to public health, the Task Force recommended against its use to screen men younger than 75 years old for prostate cancer and reclassification to a grade "D" test (3). In reclassification of PSA screening, the USPSTF changed their recommendation from their prior "I" Statement in 2008 (25). The "I" Statement indicated that current evidence was insufficient to assess the balance of benefits versus harms; and if the test is offered, patients should understand the uncertainty of the balance of benefits and harms.

Albeit, the USPSTF evidence–based recommendation against its use of PSA screening of asymptomatic men younger than 75 years, and even the recent results from the follow up of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial showing no evidence at 13 years of a mortality benefit of PSA screening (26), many have and continue the mantra “get screened, get treated and get cured” and raise objections for the necessity of the continuance of PSA screening or at least reclassification to a Grade “C” test (provide the test only if considerations support offering it), including ways to reduce overdiagnosis and overtreatment. These include:

- **PSA screening is necessary as the incidence of prostate cancer continues to increase.** This is the antithesis of an “oxymoronic statement.” The incidence of prostate cancer continues to increase because we are screening for an age-related disease with a test that is not cancer-specific but reflects any abnormality of the prostate.
• A reduction between the rate of metastatic disease on diagnosis in the pre- versus post-PSA era of 25% in 1980 versus 4% in 2002 (27). However, with the harm from overdiagnosis 30 to 100 times the estimated benefit (28) resulting in less than 0.1% (1 of 1000 screened) reduction in prostate cancer mortality over 10 years (29) and with over 2 decades of PSA screening, one cannot help but wonder what cost we are willing to pay for such a small benefit.

• PSA screening should continue to be routinely used for African-Americans as the incidence and aggressiveness of prostate cancer are greater for African-Americans than white Americans. However well intended and as recently considered (30), in 2007, the proportion of deaths among U.S. men attributed to prostate cancer was 3.3% versus 2.3% among blacks and whites, respectively. The rates are close enough that race-specific distinctions for screening are not warranted.

• Risk stratification of patients with a PSA >10 ng/mL. The basis for this is preliminary analysis of data from a subgroup of patients in the Prostate Cancer Intervention Versus Observation Trial (PIVOT; ref. 31) suggesting a reduction in prostate cancer–specific mortality of surgery versus observation in a small percentage of high-risk patients with a PSA >10 ng/mL. The question here, is in the absence of population screening, how does one select patients with a PSA >10 ng/mL?

• The use of informed decision making. Certainly paramount in any type of screening, and in PSA screening, the question of whether it can be realistically accomplished has been recently considered (30). However, even if it can, does it matter with a test slightly better than the flip of a coin?

• Prostate cancer–specific mortality has decreased since the advent of PSA screening. In general, the association between prostate cancer–specific mortality and PSA screening in studies other than those reviewed by the USPSTF (3) in various geographic areas have not been realized. For example, in looking at the impact of PSA screening in Seattle and Connecticut over 15 years, where the intensity of screening and treatment was higher in Seattle, WA, the prostate cancer–specific mortality was virtually identical (1.02 Seattle vs. Connecticut (32)). Factors likely to have contributed to a decrease in prostate cancer–specific mortality other than PSA screening, include the following:

• Improvement in surgical techniques and paradigms of treatment modalities.

• Healthier patients with increased life expectancies.

• Increased awareness resulting in more symptomatic men going to their family physician with subsequent referral to an urologist.

• More definitive attribution of death.

• And, in general, recent data show a decrease in mortality across the board in most cancers.

With the continued use of PSA screening in the manner so used, prostate cancer affects hundreds of thousands of men each year, leaving far too many with a compromised quality of life following treatment that is not going to help the majority live longer. These men deserve far more. The Task Force recommendation will hopefully lead us to look at more fruitful endeavors toward identifying men who will benefit from early diagnosis and treatment for prostate cancer, wherein multiple groups, including myself, are actively pursuing new biomarkers. In the interim of the clinical validation of these markers, we will hopefully see advances in treatment, including personalized (33), with a decrease in attendant morbidities and mortality.

Disclosure of Potential Conflicts of Interest

R.J. Ablin is a consultant of various law firms for medical malpractice cases.

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