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An Approach Using PSA Levels of 1.5 ng/mL as the Cutoff for Prostate Cancer Screening in Primary Care.

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Abstract

Prostate cancer screening with prostate specific antigen (PSA) is a controversial strategy – it reduces mortality but comes at high cost in terms of over-diagnosis and overtreatment, particularly of low-grade prostate tumors.[1] Due to considerable conflict within the literature and lack of prospective randomized studies comparing different screening protocols, recommendations differ across organizations regarding the frequency of screening, the age to start screening, interpretation of the screening results, and the diagnostic protocol to follow. However, many suggest that shared decision making must occur between the patient and the provider before any testing is done. In this paper, we propose an approach in which the shared decision-making is restricted to men found to have higher PSAs. Primary care physicians, including internists, order approximately 90% of all PSA screening tests, and shared decision-making may present logistical challenges in this context. Evidence suggests that shared decision-making is difficult and many primary care physicians struggle with it. A straightforward and clinically feasible schema for screening decisions in primary care would be highly beneficial. A level PSA of <1.5 ng/ml constitutes a very low risk category for developing aggressive prostate cancer within 5 years or more. A suggested approach to PSA testing is to use 1.5 ng/ml as a clinical threshold, restricting further discussions or workup (i.e. biomarkers) to those above that threshold. Individuals with a PSA below this threshold can be offered rescreening in approximately 5 years, depending on life expectancy. This manuscript aims to provide guidance to physicians including primary care regarding PSA screening.

Introduction: A Historical Perspective on Prostate Specific Antigen (PSA) Screening

Prostate Cancer Epidemiology

Prostate cancer is the most commonly diagnosed malignancy in males, but has one of the lowest percentage mortality compared to other cancers. An estimated 180,890 new cases of prostate cancer are expected to be diagnosed in 2016 and 26,120 men are expected to die from the disease. A significant dichotomy exists between the lifetime risk of being diagnosed versus dying from the disease. 17% of US males are diagnosed with prostate cancer within their lifetime, while only 3% die from the disease.[2] The prevalence is highest in African American men, who also have a higher risk of mortality from prostate cancer. Caucasian males have the next highest risk, while incidence is lower among those of Asian descent.

Historical Perspective on PSA Screening

Historically, there have been two ways to screen for prostate cancer: the digital rectal examination (DRE) and PSA blood test. In 1986, the Food and Drug Administration (FDA) approved PSA to be used in monitoring prostate cancer recurrence. In 1994, PSA was approved for screening, and was historically used in conjunction with the DRE.

Screening with PSA has several limitations. Many men who do not have prostate cancer will screen positive and require a biopsy to rule out cancer, while a few men with aggressive prostate cancer have low PSA. Because many prostate cancers grow so slowly that they never threaten a patient's life, there is a danger of overtreatment if these cancers are detected. This is a particularly important issue since treatment for prostate cancer is often associated with significant side effects. Our emphasis going forward should be finding the more aggressive cancers, while avoiding biopsy in those at low risk of cancer or those with indolent disease.

Current Screening Recommendations and the Evidence

Prostate Cancer Screening

Screening is defined as the process of identifying apparently healthy people who may be at increased risk of a disease or condition. Current strategies for managing prostate cancer are mainly aimed at early detection. The potential risks incurred by screening, diagnosis, and the resulting over-treatment of prostate cancer have been well documented within the literature[3]. These include erectile dysfunction, incontinence and other complications from biopsies, surgery, radiation, or androgen deprivation therapy. The majority of the harms associated with over-treatment occur in men in whom prostate cancer would not have been detected in their lifetime had it not been for screening.[4] However, rates of active surveillance are rising rapidly across the globe.[5, 6] Conversely, discontinuing screening altogether has been projected to increase the rates of metastatic disease[7] and will preclude the opportunity for many men to receive life saving intervention. Given the substantial advantages and disadvantages associated with historical screening and management paradigms, many treating providers have been left without a clear roadmap.

Screening Guidelines

Screening recommendations from various organizations differ widely. The USPSTF and Canadian Task Force on Preventive Health Care have recommended against any screening for men of all ages, while most other organizations recommend some variation of shared decision-making. The American Urological Association does not recommend routine screening for men ages 50-55, but recommends shared decision-making for men ages 55-69. The AUA further mentions that 2 year intervals can be considered to reduce harm.[8] NCCN recommends a risk-based screening algorithm, including the patient's age (screening should be considered at age 45; in the later 40s 1.0 ng/ml is recommended by NCCN as a cutoff for screening within 2 years). Notably DRE is no longer first line in the 2015 NCCN guidelines.

Data from separate European and American randomized screening trials showed divergent results. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer

Screening Trial did not show convincing evidence that PSA screening reduces prostate cancer mortality. However, a large majority of men in the control group also received PSA testing before and/or during the study so it was not comparison of screening vs. no screening but rather of organized versus opportunistic screening. The European Randomized Study of Screening for Prostate Cancer (ERSPC) found that screening reduces metastasis and prostate cancer death, but also leads to over-diagnosis. In both of these trials, biopsy was recommended based on a fixed PSA threshold. An alternate approach to a fixed screening protocol is to use a risk-adapted approach. For example, Thompson et al suggested that optimal PSA screening frequency for men with a PSA level of 0.1 to 1.0 ng/ml might be up to every 10 years. This approach has the potential to dramatically reduce the cost of screening, decreasing over detection of inconsequential tumors, while maintaining detection of tumors for which treatment has been proven to reduce prostate cancer mortality.[9]

Screening in the Primary Care Setting

Today, after nearly three decades since PSA was first used as a tool for the early detection of prostate cancer, substantial uncertainty surrounds its use. Shared decision-making is ideal but may be difficult to implement in the primary care setting due to several factors, including: the limited time and availability that primary care clinicians have for in-depth discussions about the pros and cons of PSA testing, given the numerous other issues typically covered in a visit; the wide range of information and data that could be discussed during each visit; and the complex tradeoff between immediate harms and long-term benefits.[10] Furthermore, it is important to note that shared decision making rarely occurs with many tests performed by PCPs – often times, it only occurs after an abnormality is detected.

In some cases, spending considerable amounts of time in discussions about PSA may be seen as an inherent bias towards screening and could result in reducing the time spent on other preventive services, thereby resulting in an opportunity cost. Studies have found that only about half of primary care physicians are compliant with recommendations to discuss screening with eligible patients, with a large proportion

adopting a default “screen all” or “screen none” approach.[11] The value of a “detailed discussion” about PSA depends critically on the primary care providers’ knowledge. Less than one in five primary care providers report confidence in their knowledge about PSA, with a low correlation between confidence and actual knowledge.[12, 13] A recent article in JAMA by Eggener et al acknowledged that a novel approach to prostate cancer screening is needed because of the workflow limitations in "discussing this complex decision" in the PCP office.[10, 14] Assuming that some element of screening is embraced, there is a need to develop a simple/easy algorithm regarding the role of PSA in PC screening and to assess when further diagnostic tests are needed.

A New Perspective on PSA Screening in the Primary Care Setting

Rather than the fixed one-size-fits all approach used for screening in the past, there may be ways to use PSA more intelligently for more personalized decisions. We need to avoid PSA tests in men who would have little to no gain by focusing on age and health. Several authors have targeted the relative risks of a baseline PSA and subsequent risk of an abnormal level of greater than 4 in 5 years.[15, 16] In a 2011 article, Crawford et al found that a PSA of <1.5 ng/ml constitutes a very low risk category for developing prostate cancer (particularly high risk disease) within 4-5 years[17]. In a follow up piece, they suggested embracing the 1.5 ng/ml level and only having further discussions or workup with those above that threshold. An elevated PSA (>1.5ng/ml), becomes case finding (with a focus on identifying men who have a higher risk of having clinically significant disease). In such a case where there is increased suspicion of clinically significant disease, informed-decision-making should be employed, as several options are available as next steps. These options include following up with the patient in 6 months or 1 year, referral to a urologist, or using new techniques, such as MRI or biomarkers to determine whether the patient is at risk of harboring clinically significant disease. For those below the level, recommendations were made to screen again in 5 years. Potential benefits of this approach include reducing the cost of screening, decreasing over detection of inconsequential tumors, and maintaining detection of tumors for which treatment has been proven to reduce prostate cancer mortality.[9]

Some suggest that a change in screening that leads to the biggest health gain is to stop screening older men. This applies to the majority of men over 70 and those over 60 with low PSA (e.g. < 1.5) when they get to the age of 60.[18, 19] Indeed, Lilja et al found that a single PSA measured in white men between 44- 50 years was highly correlated with any cancer, palpable disease and advanced cancer. At a PSA threshold of 1.5 ng/ml theses values were approximately 20%, <15%, and 5% respectively 20-25 years after blood drawn when they were 44-50 years of age. Similarly Vickers et al showed that for white men with a PSA in the highest 10th grouping (i.e., 1.6ng/ml or greater) at age 45-49 contributed to nearly half of all prostate cancer deaths over the next 25-30 years. They further postulated that low risk men based on baseline PSA might only need three PSA measurements in their lifetime (i.e., 40s, 50 and age 60). Little is known, however, whether these long-term data apply to men of other racial and ethnic groups.[20, 21] Crawford et al showed however that at least over a 4 year period both Caucasian and African American men were at low risk for any cancer diagnosis (i.e., 0.51,0.54% respectively) when their baseline serum PSA level was less than 1.5 ng/ml.[17] Of note, among both African American and Caucasian men a substantial majority of PSA values were less than 1.5ng/ml (79 and 80% respectively).[17]

Next Generation of Clinical Decision Making Tools

Under the proposed paradigm (Figure 1; Supplemental Figure 1), PSA can be performed as part of a regular blood panel and only men with a PSA ≥ 1.5 ng/ml require shared decision-making about further testing and diagnostic evaluation. This will greatly limit the number of men requiring such a discussion and can be performed either by the PCP or by referral to a urologist. Men with elevated PSA levels should be evaluated for benign causes. Repeat testing of PSA and secondary tests such as SelectMDx, 4KScore, PHI, mpMRI can be used to refine the specificity of screening to detect high-risk disease. Sampling error is an inherent and well-documented issue with false-negative rates of prostate biopsy procedures reported as high as 25-35%.[22, 23] This results in repeat biopsies, which are associated with additional risks of infection and hospitalization, and with significant costs.

Conclusion

Although many organizations now recommend shared decision-making when it comes to PSA testing, this can present many logistical challenges in daily clinical practice and is not always realistic. Furthermore, we acknowledge that several groups recommend for informed decision-making to take place before the PSA test is ordered. However, our aim is to draw a parallel to what happens in the real world for primary practice physicians – i.e., informed decision-making typically comes after the test results (be it blood sugar, blood pressure, cholesterol, or in this case PSA) are known. We believe that a simple message using a PSA cutoff of 1.5 ng/ml is reflective of what family practice physicians often experience in their practices with conditions such as mild hypertension and pre-diabetes. In this paper, we have presented an alternative approach in which screening is performed for men with at least a 10-year life expectancy. If the PSA is less than 1.5 ng/ml, consider a 5-year re-screening interval. If the PSA is 1.5 ng/ml or greater, or the PCP identifies an abnormality on DRE, refer to a specialist or consider a biomarker to assess risk more precisely. This algorithm is similar to that utilized for an elevated blood sugar, where an abnormal result triggers another test such as an A1C hemoglobin. In our algorithm, we recommend that a biopsy should not be performed unless the risk of an aggressive tumor is significant, and following a thorough discussion of benefits and risks with the patient. These discussions should emphasize that the purpose of screening is the early identification of potentially lethal disease, and that in most cases low-risk tumors, if identified, do not require immediate treatment. A potential benefit of this approach is that it could greatly reduce the number of men requiring shared decision-making and further testing to those at greater risk of significant prostate cancer.

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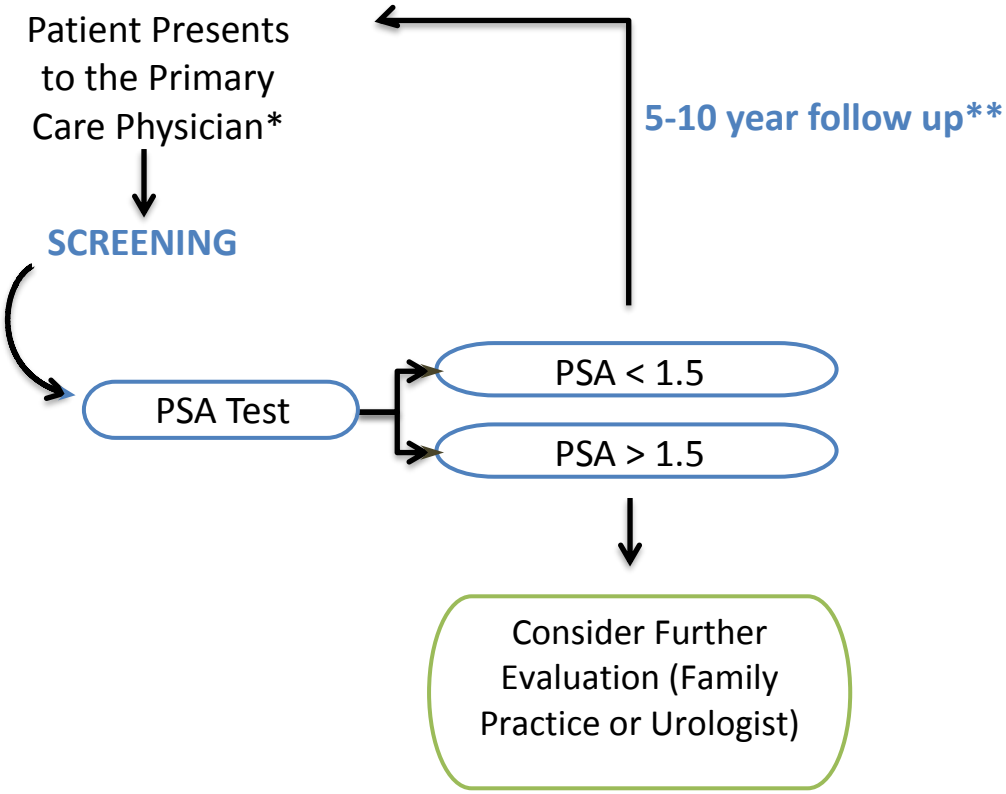
Figure 1: Role of PSA Testing in the Prostate Cancer Diagnostic Pathway within a Primary Care Setting



* Begin age 45-65 with 10-year life expectancy.

**< 1 10 years –see text

Supplemental Figure 1: Approach to Shared Care in Prostate Cancer Diagnosis