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Guideline of guidelines: prostate cancer screening

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Introduction

Prostate cancer screening is one of the most controversial topics in urology [1]. On one hand, there is randomised data showing that PSA screening results in earlier stages at diagnosis, improved oncological outcomes after treatment, and lower prostate cancer mortality rates. However, the downsides include unnecessary biopsies due to false-positive PSA tests, over-diagnosis of some insignificant cancers, and potential side-effects from prostate biopsy and/or prostate cancer treatment. The ongoing controversy is highlighted by the divergent recommendations on screening from multiple professional organisations. The purpose of this article is to summarise the recent guidelines on prostate cancer screening from 2012 to present.

The United States Preventive Services Task Force (USPSTF)

The USPSTF is a group of health experts that makes recommendations about preventive healthcare [2]. In 2008, this group recommended against PSA screening for men aged ≥75 years [3]. At that time, they felt that the evidence was insufficient to make a recommendation on screening in men younger than 75 years.

In 2012, the USPSTF updated their literature review and instead issued a Grade D recommendation against prostate cancer screening for men of all ages [2]. The rationale that they gave for this is that for every 1000 men screened, there would be only one fewer prostate cancer death but 30–40 men with incontinence or erectile dysfunction due to treatment, two with serious cardiovascular events, and one with venous thrombosis.

There was significant controversy surrounding this recommendation. For example, the AUA issued a statement 'that the USPSTF, in disparaging the PSA test before a newer diagnostic is more readily available, does a great disservice to American men and may cause more harm than good' [4]. The AUA stated that it was 'inappropriate and irresponsible to issue a blanket statement against PSA testing, particularly for at-risk populations such as African-American men and those with a family history of the disease', and that the USPSTF had 'overstated the harms and underestimated the benefits of prostate cancer testing'. Indeed, recent data suggests that the rates of PSA screening in the USA have decreased since the USPSTF recommendation [5].

The AUA

When the USPSTF recommendation was issued, the AUA itself was already in the process of updating its own guidelines on prostate cancer screening/early detection using the Institute of Medicine framework [6]. Specifically, they commissioned an independent group to perform a systematic review of articles published from 1995 to 2013. The results of this literature review were used to issue a series of Recommendations, Standards and Options, for which the underlying evidence base was graded from A (high) to C (low).

The new guidelines were issued in May 2013 and were specifically intended for use by urologists. First, the AUA recommended against PSA screening in men aged <40 years due to a low overall prevalence of prostate cancer in this age group and potential for harm through screening (Recommendation; Evidence Strength Grade C). They also did not recommend *routine* screening for average-risk men aged 40–54 years (Recommendation; Evidence Strength Grade C). However, they recommended individualised decisions about screening for higher risk men aged <55 years, such as those with a positive family history and African-American men.

For men aged 55–69 years, the AUA recommended shared decision-making about screening (Standard; Evidence Strength Grade B). Although this group had the strongest evidence for screening benefit, there remains potential for harm. For this reason they emphasised the importance of a bilateral discussion about screening between the patient and physician including the benefits, risks, uncertainties and the patient's values/preferences. Meanwhile, the AUA recommended against

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performing PSA screening as part of health fairs or other settings where this type of shared decision-making is not available.

The AUA also stated that a routine screening interval of ≥2 years may be preferred over annual screening to reduce harms (Option; Evidence Strength Grade C), but that the baseline PSA level could be used to help inform the screening interval. Finally, the AUA recommended against *routine* PSA screening in men aged ≥70 years or with a life expectancy of <10–15 years (Recommendation; Evidence Strength Grade C), acknowledging that some men aged > 70 years in excellent health may still benefit from screening.

It is noteworthy that these guidelines apply specifically to screening in the asymptomatic population. They do not address diagnostic PSA testing in symptomatic men, and do not incorporate 'secondary screening tools', such as proenzyme PSA (proPSA), human kallikrein 2 (hK2), prostate cancer antigen 3 (PCA3) and multivariable nomograms, which were not tested in the randomised trials. The AUA panel recognised that these tests may have utility for making decisions about prostate biopsy, but that they have not been definitively proven to increase the benefit-to-harm ratio.

The American College of Physicians (ACP)

In May 2013, the ACP also published a new guidance statement on screening for prostate cancer based on an appraisal of existing guidelines from the National Guideline Clearinghouse [7]. For men aged 50–69 years, the ACP recommended informing patients about the 'limited potential benefits and substantial harms of screening for prostate cancer'. The decision about screening should be then be based upon the patient's preferences after a discussion of benefits and harms, taking into consideration their prostate cancer risk factors, life expectancy and general health status.

Meanwhile, the ACP recommended against screening for men aged <50 and >69 years or with a life expectancy of <10–15 years. Similar to the AUA, the ACP did not address the use of adjunctive PSA measurements, e.g. free PSA, PSA density or PSA velocity, as they were not evaluated in the clinical trials of screening.

The European Association of Urology (EAU)

The EAU subsequently performed an independent systematic review of the published literature from 1990 to 2013, and updated its own recommendations for prostate cancer screening [8]. First, they concluded that PSA screening reduces prostate cancer mortality based on the European Randomized Study of Screening for Prostate Cancer (ERSPC) and Goteborg randomised population-based screening trial. Next, they stated that screening reduces the risk of being diagnosed with or developing advanced disease during follow-up.

Unlike the AUA, the EAU recommended obtaining a baseline PSA measurement at age 40–45 years, as these measurements predict the risk of future life-threatening disease [9,10]. Moreover, they recommended that the baseline PSA measurement should be used to inform the screening interval. For example, they suggested a screening interval of 2–4 years if the baseline level is >1 ng/mL; whereas a longer interval up to 8 years could be used for men with a lower baseline PSA level.

The EAU recommended that PSA screening should be offered to men with a life expectancy of ≥10 years, independent of the chronological age. Finally, the EAU guidelines recommend integrating a multivariable approach into the decision-making process in the future. Although PSA is the most important parameter for assessing prostate cancer risk, other risk factors such as ethnicity and family history should be taken into consideration. They highlight the availability of several prostate cancer risk calculators that incorporate multiple variables.

The Melbourne Consensus Statement

Considering the multiple conflicting recommendations described above, a group of international experts convened at the Prostate Cancer World Congress in August 2013 to create a set of consensus statements intended to provide clarity for patients and physicians [11]. The first consensus was that Level 1 Evidence shows a reduction in metastatic disease and prostate cancer mortality for men aged 50–69 years. This is based on the ERSPC [12] (starting at age 55 years) and Goteborg randomised trial [13] (starting at age 50 years). Correspondingly, the Melbourne Consensus Statement recommends that healthy men in this age group should be informed about the positive and negative aspects of PSA testing in a shared decision-making process. Nevertheless, the Melbourne Consensus statement emphasises that prostate cancer diagnosis must be uncoupled from prostate cancer intervention. While screening is important to identify high-risk cases, men with lower risk disease may not require aggressive intervention.

Similar to the EAU guidelines, the Melbourne Consensus statement recommends that PSA testing should not be considered on its own, but rather as part of a multivariable approach to prostate cancer detection. Also similar to the EAU, the Melbourne Consensus Statement recommends baseline PSA testing of men in their 40 s to predict the future risk of prostate cancer and its aggressive forms. Although such a strategy was not tested in the randomised screening trials, they reference strong observational data on the utility of baseline PSA measurements and suggest incorporating this information into the shared decision-making process. Finally,

Key Points

- Randomised trials have shown that PSA screening reduces metastatic prostate cancer and disease-related death.
- The USPSTF recommends against PSA screening, while most other professional organisations recommend shared decision-making about PSA screening.
- PSA screening should be discontinued for men with <10-year life expectancy.
- Several guidelines now recommend baseline PSA testing for men in their 40 s for risk stratification.
- Some guidelines also suggest a risk-adapted approach to screening considering multiple risk factors along with PSA for clinical decisions.

the Melbourne Consensus Statement recommends that older men with a > 10-year life expectancy should not be denied PSA screening based on chronological age.

Conclusion

Since 2012, there have been several new guidelines on prostate cancer screening. At one extreme, the USPSTF recommended against prostate cancer screening for men of all ages. Most other groups instead recommend shared decision-making about screening for men with at least a 10-year life expectancy, including a discussion of risks, benefits, uncertainties, and patient preferences. However, there is disagreement between the various guidelines about the age to initiate this discussion, the optimal screening interval, and the use of secondary tests. Both the EAU Guidelines and Melbourne Consensus Statement recommend offering baseline PSA testing to men in their 40 s and using this to guide the screening protocol. The ACP and AUA recommend shared decision-making about screening for men aged 50–69 and 55–69 years, respectively. Some guidelines suggest the use of a multivariable approach to screening considering other risk factors along with the total PSA level, although this type of protocol was not tested in the major randomised trials.

Conflicts of Interest

S.L. received an honorarium for lecturing at the Interactive Genitourinary Cancer Conference (IGUCC) sponsored by Sanofi.

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Abbreviations: ACP, American College of Physicians; EAU, European Association of Urology; ERSPC, European Randomized Study of Screening for Prostate Cancer; USPSTF, United States Preventive Services Task Force.