Published in final edited form as:

Urology. 2016 May ; 91: 12–18. doi:10.1016/j.urology.2015.12.054.

The Memorial Sloan Kettering Cancer Center recommendations for prostate cancer screening

Andrew J. Vickers, James A. Eastham, Peter T. Scardino, and Hans Lilja

Memorial Sloan-Kettering Cancer Center

Abstract

The Memorial Sloan-Kettering Cancer Center (MSKCC) recommendations on prostate cancer screening were developed in response to three limitations of previous screening guidelines: insufficient evidence-base, failure to link screening with treatment, and lack of risk stratification. The objective of the recommendations is to provide a schema for prostate cancer screening that maximizes the benefits, in terms of reduction in prostate cancer-specific mortality, and minimizes the harms, in terms of overdiagnosis and overtreatment. We recommend the following schema for men choosing to be screened following informed decision-making. Starting at age 45, PSA without DRE. If PSA ≥ 3 ng / mL: consider prostate biopsy; PSA ≥ 1 but < 3 ng / mL: return for PSA testing every 2 – 4 years; PSA < 1 ng / mL: return for PSA testing at 6–10 years. PSA testing should end at age 60 for men with PSA ≥ 1 ng / mL; at 70, unless a man is very healthy and has a higher than average PSA; at 75 for all men. The decision to biopsy a man with a PSA > 3 ng / mL should be based on a variety of factors including repeat blood draw for confirmatory testing of the PSA level, DRE results, and work-up for benign disease. Additional reflex tests in blood such as a free-to-total PSA ratio, the Prostate Health Index, or 4Kscore, or urinary testing of PCA3, can also be informative in some patients. The best evidence suggests that more restricted indication for prostate biopsy and a more focused approach to pursue screening in men at highest risk of lethal cancer would retain most of the mortality benefits of aggressive screening schema, while importantly reducing harms from overdetection and overtreatment.

Keywords

prostate cancer; PSA; screening; detection; informed consent

Corresponding Author: Andrew Vickers, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, US, vickersa@mskcc.org.

Declaration of interests: Hans Lilja holds patents for free PSA, hK2, and intact PSA assays, and is named, along with Andrew Vickers, on a patent application for a statistical method to detect prostate cancer. The method has been commercialized by OPKO. Lilja, Vickers and Scardino receive royalties from any sales of the test. Dr Vickers has stock options in OPKO.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

The Memorial Sloan-Kettering Cancer Center (MSKCC) recommendations on prostate cancer screening were originally developed in 2011 as a response to what we felt were major limitations of other screening guidelines available at the time. First, many guidelines were not sufficiently evidence-based. For instance, several guidelines recommended annual screening despite the lack of evidence that this was superior to biennial or less frequent screening, or recommended prostate-specific antigen (PSA) velocity as a biopsy indication in men with a PSA below recommended cut-points, despite lack of data demonstrating that this would do more good than harm. A second problem with contemporary guidelines was that no explicit link was made between screening and treatment. We see this as a critical deficit, as most of the benefits and harms of screening do result from subsequent treatments, not directly from the PSA test itself. Third, few guidelines used risk stratification. For instance, a man aged 52 with a PSA of 2 ng / ml is at very much higher risk of an aggressive prostate cancer than a 52-year old man with a PSA of 0.4 ng / ml, yet most guidelines would recommend identical advice for both patients, such as repeating digital rectal exam (DRE) and PSA-testing the following year. Our original set of recommendations set out to remedy each of these three failings: being evidence-based, linking PSA testing to treatment, and focusing on risk stratification.

In this paper, we provide an update of our recommendations in the light of evidence that has emerged in recent years.

Methods

The objective of the guideline is to provide a schema for prostate cancer screening that maximizes the benefits, in terms of reduction in prostate cancer-specific mortality, and minimizes the harms, in terms of overdiagnosis and overtreatment. The clinical questions covered by the guideline include the age at which screening should start and cease; the frequency at which screening should be repeated; whether initial screening should be based on the digital rectal exam, PSA testing only, or both; and the indications for biopsy. The primary target group for the guideline is men in good health aged 45 or over who do not have genitourinary symptoms or prostate disease. Our rationale for stating merely that men be “in good health” rather than, as many guidelines state, having a minimum life expectancy such as 10 years, is that the 10 year cut-off, has never been adequately justified, indeed, empirical data suggest that the major benefits of screening accrue beyond ten years¹. Moreover, most doctors are poor judges of life expectancy². The intended audience of the recommendations is primary care physicians, internists and urologists. While most screening takes place in primary care, urologists have both a clinical and educational role in screening decisions.

With respect to the evidence base of the recommendations, there have been justified calls for the use of systematic methods to search for and select evidence³. This is a methodology that we respect, as illustrated by our record of publishing systematic reviews and meta-analyses. That said, the value of only using systematic review methodology to the current task is less clear. With respect to the question of whether to screen at all, the major randomized trials

and modeling studies on PSA screening are well known. With respect to questions such as the frequency of PSA testing, or indications for biopsy, we question the value of a systematic review of the literature. We believe that any attempt to use systematic literature search to address such questions would be highly imprecise, leading to a large volume of literature, much of which would be uninformative.

Our approach to the evidence base was to focus on three well-known high quality studies. It is natural to include the European randomized screening for prostate cancer (ERSPC), on the grounds that this provides the major evidence that PSA screening reduces mortality in men who would not otherwise be screened¹, a question which, do to high use of PSA in the control group, could not be addressed in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial in the US⁴. Second, we use data from the control arm of the Prostate Cancer Prevention Trial (PCPT)⁵. This study is unique in that all men enrolled in the trial were biopsied irrespective of indication or PSA-level. The third study we used is the Malmö Preventative Project study (Malmö cohort) on the grounds that this cohort is based on a large, highly representative set of middle aged men providing cryopreserved blood before the PSA-test became available⁶. The Malmö cohort is uniquely well suited to determining the relationship between PSA levels and very long-term risk of carefully ascertained clinical cancer endpoints (such as cancer-specific mortality) in an unscreened population. The findings are similar to many other comparable studies in the literature – see, for instance, the review by Loeb et al.⁷ – but are unique in terms of the size of the cohort and the precision with which clinically relevant estimates can be derived. One possible drawback of the Malmö cohort is that the prostate cancer mortality rate is somewhat higher in Sweden than in the US. However, we use the Malmö cohort with respect to relative risk – for instance, that a high proportion of early deaths from prostate cancer occur in men with the highest PSAs at age 45 – 49 – and identifying patients at low risk for longer screening intervals or early cessation of screening, in which case, overestimation of risk is conservative.

For a limited number of uncontroversial areas, the main results from these three key study cohorts were complemented by other data. First, one of the main concerns with prostate cancer screening is overdiagnosis. Data supporting that age is strongly associated with overdiagnosis were obtained from US national incidence statistics⁸. Second, two recommendations as to indication for biopsy follow routine clinical practice in the US: repeating the PSA to check that it remains elevated and work-up for benign disease. Data supporting these practices were obtained from a well-known study on PSA fluctuations⁹, and a comparison¹⁰ between US clinical cohorts versus those from the ERSPC, and the ProtecT-trial¹¹ in the UK: this comparison shows a higher yield of positive biopsies in the US suggesting that US clinical practice aids the discrimination of benign from malignant PSA elevations. Third, it is commonly recommended that low-risk cancer should initially be managed conservatively. Data on how the value of treatment varies by patient risk were obtained from the two randomized trials of surgery for localized prostate cancer, SPGG4¹² and PIVOT¹³. Fourth, our recommendation that treatment should preferably occur at a high-volume provider follows an extensive literature on the volume-outcome relationship^{14,15}. Finally, several aspects of the recommendations follow three widely accepted assumptions made in all areas of medicine: that informed consent should be given for important decisions, that outcomes are improved if medical decisions are congruent with patient

preference, that patient behavior is modified by knowledge of risk, and that the ratio between benefits and harms will be maximized if efforts focus on those at highest risk.

The evidence for each recommendation statement is given in the Supplementary Appendix.

Results

We recommend PSA screening only if an informed discussion between the patient and doctor has taken place and the man has subsequently agreed to screening. Noting that an “informed discussion” is a rather open-ended concept, and could potentially involve many hours and expert knowledge, we have separately published a simple guide to inform such discussions¹⁶. This emphasizes the possibility that screening will detect low risk prostate cancers and that such cancers do not require immediate treatment. The decision whether to screen or not hinges on the patient’s tolerance for an active surveillance approach. Our recommendations therefore start from the position that a screen-detected prostate cancer should be *information* to help decisions, not an *indication* for immediate treatment. Indeed, prostate cancer screening is only likely to do more good than harm if active surveillance is the routine initial management approach for low risk disease, and that higher risk disease is subject to curative treatment, preferably at a high volume hospital.

The scheme for testing is shown in figure 1. One key part of the recommendations is that an elevated PSA is not, in itself, an indication for biopsy. The conventional PSA test lacks specificity, that is, most men with a modest PSA elevation do not have evidence of clinically significant prostate cancer at biopsy. The recommendations state that a PSA ≥ 3 ng / mL indicates that biopsy should be *considered*. Additional factors that affect the decision of whether to biopsy are given in table 1. Some aspects of the recommendations involve clinical judgment. For instance, recommendation is for screening every 2 – 4 years for men with PSA levels of 1 – 3 ng/mL. A physician may choose to recommend a four-year interval for an older man with a PSA close to 1 ng/mL, or an interval of 2 years or less for a younger man with a PSA closer to 3 ng/mL.

The recommendations involve risk stratification, for instance, the frequency of screening during a man’s 50’s depends on his PSA level. We also believe that men should be informed of their risk. A 52 year-old man with a PSA of 2 ng/mL, which is in the top 10% at that age, has a close to a ten-fold higher risk of a subsequent life-threatening prostate cancer than a man of similar age who has a PSA of 0.4 ng/mL, below the age-specific median¹⁷. The previous approach has been to inform both men that PSA results were “normal” and that they should return for annual testing. Instead, the man with the PSA of 2 ng/mL should be informed that, although there may be no need for an immediate biopsy, he is in a higher than average risk category, and should get his PSA checked regularly (e.g. every 2 years). This is so that, were he to develop prostate cancer, it could be diagnosed early. The man with PSA of 0.4 ng / mL, on the other hand, can be reassured that he is at low risk and would not benefit from repeat PSA testing for several years.

With respect to treatment of screen-detected localized prostate cancer, we strongly recommend active surveillance as the preferred approach for men with low-risk disease.

Although this is typically defined in terms of clinical stage, tumor grade at biopsy, and PSA - Gleason score 6, T1c or T2b, and PSA < 10 ng / – ml we note that PSA and stage are relatively weak predictors of mortality¹⁸. Typical practice at MSKCC is to offer active surveillance to most patients with Gleason 6, as well as some with Gleason 3 + 4 who have low volume pattern 4 disease.

Recent years have seen increased interest in the use of Magnetic Resonance Imaging (MRI) in the biopsy setting. At MSKCC, MRI is used clinically to determine needle placement for some diagnostic biopsies, and to determine the need for repeat biopsy for some patients on active surveillance. However, both such uses fall somewhat outside the scope of these recommendations. Given the current state of the evidence, we do not recommend MRI to help determine whether diagnostic biopsy is indicated, although we await the results of studies such as the UK PROMIS trial.

On a final note, the recommendations are a guide, not a rule. There will always be a need for exceptions to be made based on reasonable clinical judgment. For instance, a patient with a very strong family history of prostate cancer might reasonably be considered for a PSA test at age 40; a young man who is very risk averse might reasonably be considered for biopsy at a PSA less than 3 ng / mL.

Discussion

The MSKCC recommendations constitute a relatively minimalist approach to early detection and treatment of localized prostate cancer. After an informed discussion that emphasizes the risk of overtreatment, most men accepting screening should have only three lifetime PSA tests. Biopsy is restricted to men with an elevated risk of high-grade cancer. A substantial proportion, perhaps a majority, of screen-detected cancers can initially be managed conservatively. We believe that such an approach will not only decrease the harms of PSA screening, in terms of overdiagnosis and overtreatment, but will increase the benefits. This is not only because we focus screening on a subset of men at highest risk of life-threatening prostate cancer, but because we believe the doctors and patients will have better compliance to a less burdensome screening approach.

The MSKCC recommendations involve risk stratification and may therefore appear to be somewhat more difficult to apply in practice than a “one size fits all” approach, such as yearly screening for all men aged 50 – 70. We believe that a risk-stratified approach will lead to better patient compliance than “one size fits all”. Moreover, we have tried to keep a relatively consistent form and if recommendations relating to clinical judgment are removed (for men above 70 and men aged 60 – 70 with a PSA of 1 – 2 ng/mL), the recommendations can be simplified to an easy to remember algorithm: PSA test from 45 – 70 with possible biopsy for PSA ≥ 3 ng / ml, regular screening for men with PSA = 1 ng / ml and < 3 ng / ml, infrequent screening ending at age 60 for men with PSA < 1 ng / ml. In our view, such a schema will retain most of the mortality benefits of more aggressive screening approaches, while importantly reducing the harms.

Differences between the MSKCC recommendations and formal guidelines from professional societies have become less obvious over the last few years. For instance, prior iterations of the American Urologic Association (AUA) and National Cancer Center Network (NCCN) guidelines previously included annual screening for most men, and a wide range of indications for biopsy, such as PSA velocity and DRE. The most recent NCCN¹⁹, AUA²⁰ and EAU²¹ guidelines now also make an explicit link between screening and treatment.

Several differences between our recommendations and those of other professional groups are worth discussing. As regards starting age, the AUA recommends 55 except for African Americans or men with family history of prostate cancer; the NCCN like MSKCC recommends 45; the EAU guideline is somewhat unclear; but appears to recommend 45 for African Americans and men with a family history and 50 otherwise. Our view is that although age 55 – 69 was the “core group” of the ERSPC, the Göteborg Randomized Screening Study²² included men aged 50 – 64, clearly giving randomized support for starting screening at 50. As regards earlier screening for men at increased risk, we have demonstrated unequivocally that PSA is a far stronger risk factor than either race or family history²³. Hence, our guidelines do not suggest differential PSA screening for African Americans. That said, we also acknowledge that the net benefit of starting screening at age 45 rather than at age 50 has not been clearly demonstrated.

With respect to the age at which to stop screening, the NCCN gives age 75 or >75 in “select” patients; the AUA and EAU are close to the MSKCC recommendation of stopping at age 70 except for a subgroup of men with excellent health; the EAU gives a minimum life expectancy of 15 years, which is close to that for the average 70 year old.

For screening interval, the AUA gives screening every two years, although “intervals for rescreening can be individualized” by PSA. Like the MSKCC guidelines, the NCCN specifies different screening intervals depending on whether PSA is $\leq$ or $>$ 1 ng / mL. However, the rescreening interval is given as 1–2 years for PSA $\leq$ 1 ng / mL, and 2 – 4 years for lower PSAs, much shorter than those in the MSKCC recommendations and of an unclear provenance. The EAU suggests similar intervals to MSKCC, 2 years for “those initially at risk” and 8 years in those not at risk, although risk is not clearly defined.

The MSKCC recommendations are generally the most restrictive with respect to biopsy criteria, clearly recommending that patients must be worked up and be evaluated to be at higher than average risk of high-grade disease. The AUA and EAU guidelines are somewhat circumspect about the use of reflex tests.

The major difference between the MSKCC recommendations and those of other organizations concerns the continued screening of men of men in their 60’s with low PSA. We have clearly demonstrated²⁴ that the rather questionable observed net benefit of PSA screening is actually an average of two very different subgroups: men with a PSA above 2 ng / mL at age 60 who experience a large decrease in mortality if they are screened with relatively little overdiagnosis versus those who have a lower PSA, who experience considerable overdiagnosis but zero benefit to screening. Very similar results have been reported by a separate group of investigators using different comparison cohorts²⁵. Given the

strength and potential impact of these data, we see no justification for reticence in recommending cessation of screening for a large group of men – 50 – 75% of the population – in which harms clearly outweigh benefit.

PSA screening has engendered a long history of controversy. This controversy centers on whether the benefits, in terms of reduction in prostate cancer-specific mortality, are greater than the harms, in terms of overdiagnosis and overtreatment. We believe that a more restrictive approach to screening and treatment can mitigate many of the harms of PSA screening, but retain most of the benefits. We urge urologists, internists and primary care physicians to adopt our recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: National Cancer Institute (R33 CA127768, R01 CA160816, and P50 CA092629), the Sidney Kimmel Center for Prostate and Urologic Cancers, David H. Koch through the Prostate Cancer Foundation.

We thank the authors for their kind remarks on our paper. Perhaps the only substantive disagreement concerns the role of MRI. The view expressed in our paper was that although promising, the data are simply not sufficient to include MRI in our recommendations. The evidence presented in the editorial does not change our view. The authors cite one small study (n=100), in which MRI was found to be predictive in one rather overfit statistical model (7 variables to predict 24 events) but not in another. The second study included slightly more patients (n=223), and did have promising results. In comparison, the biomarkers that the authors mention, such as the Prostate Health Index and the 4kScore, have been validated in numerous studies including thousands of patients.

We would be delighted if the research data developed sufficiently support a role for MRI in biopsy decision making. But that is not the case at the current time.

References

1. Schroder FH, Hugosson J, Roobol MJ, et al. 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
2. Walz J, Gallina A, Perrotte P, et al. Clinicians are poor raters of life-expectancy before radical prostatectomy or definitive radiotherapy for localized prostate cancer. *BJU international*. 2007; 100:1254–1258. [PubMed: 17979925]
3. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Quality & safety in health care*. 2003; 12:18–23. [PubMed: 12571340]
4. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. *Journal of the National Cancer Institute*. 2012; 104:125–132. [PubMed: 22228146]
5. Thompson IM, Ankerst DP, Chi C, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *Journal of the National Cancer Institute*. 2006; 98:529–534. [PubMed: 16622122]
6. Lilja H, Ulmert D, Bjork T, et al. Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007; 25:431–436. [PubMed: 17264339]
7. Loeb S, Carter HB, Catalona WJ, et al. Baseline prostate-specific antigen testing at a young age. *European urology*. 2012; 61:1–7. [PubMed: 21862205]

8. Vickers AJ, Sjoberg DD, Ulmert D, et al. Empirical estimates of prostate cancer overdiagnosis by age and prostate-specific antigen. *BMC medicine*. 2014; 12:26. [PubMed: 24512643]
9. Eastham JA, Riedel E, Scardino PT, et al. Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. *JAMA : the journal of the American Medical Association*. 2003; 289:2695–2700. [PubMed: 12771116]
10. Vickers AJ, Cronin AM, Roobol MJ, et al. The relationship between prostate-specific antigen and prostate cancer risk: the Prostate Biopsy Collaborative Group. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2010; 16:4374–4381. [PubMed: 20736330]
11. Lane JA, Donovan JL, Davis M, et al. Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. *The Lancet Oncology*. 2014; 15:1109–1118. [PubMed: 25163905]
12. Vickers A, Bennette C, Steineck G, et al. Individualized estimation of the benefit of radical prostatectomy from the Scandinavian Prostate Cancer Group randomized trial. *European urology*. 2012; 62:204–209. [PubMed: 22541389]
13. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *The New England journal of medicine*. 2012; 367:203–213. [PubMed: 22808955]
14. Gruen RL, Pitt V, Green S, et al. The effect of provider case volume on cancer mortality: systematic review and meta-analysis. *CA: a cancer journal for clinicians*. 2009; 59:192–211. [PubMed: 19414631]
15. Trinh QD, Bjartell A, Freedland SJ, et al. A systematic review of the volume-outcome relationship for radical prostatectomy. *European urology*. 2013; 64:786–798. [PubMed: 23664423]
16. Vickers AJ, Edwards K, Cooperberg MR, et al. A simple schema for informed decision making about prostate cancer screening. *Annals of internal medicine*. 2014; 161:441–442. [PubMed: 25222389]
17. 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 (Clinical research ed)*. 2013; 346:f2023.
18. Fall K, Garmo H, Andren O, et al. Prostate-specific antigen levels as a predictor of lethal prostate cancer. *Journal of the National Cancer Institute*. 2007; 99:526–532. [PubMed: 17405997]
19. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection. Version 1.2015
20. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. *The Journal of urology*. 2013; 190:419–426. [PubMed: 23659877]
21. Mottet, N.; Bellmunt, J.; Briers, E., et al. *European urology*. European Association of Urology; 2015. Guidelines on Prostate Cancer.
22. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. *The Lancet Oncology*. 2010; 11:725–732. [PubMed: 20598634]
23. Vertosick EA, Poon BY, Vickers AJ. Relative value of race, family history and prostate specific antigen as indications for early initiation of prostate cancer screening. *The Journal of urology*. 2014; 192:724–728. [PubMed: 24641912]
24. Carlsson S, Assel M, Sjoberg D, et al. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. *BMJ (Clinical research ed)*. 2014; 348:g2296.
25. van Leeuwen PJ, Connolly D, Tammela TL, et al. Balancing the harms and benefits of early detection of prostate cancer. *Cancer*. 2010; 116:4857–4865. [PubMed: 20839233]

PSA without DRE for men aged:

45 – 49:

- PSA ≥ 3 ng / mL: consider prostate biopsy
- PSA ≥ 1 but < 3 ng / mL: return for PSA testing every 2 - 4 years
- PSA < 1 ng / mL: return for PSA testing at age 51 - 55

50 – 59:

- PSA ≥ 3 ng / mL: consider prostate biopsy
- PSA ≥ 1 but < 3 ng / mL: return for PSA testing every 2 - 4 years
- PSA < 1 ng / mL: return for PSA testing at age 60

60 – 70:

- PSA ≥ 3 ng / mL: consider prostate biopsy
- PSA ≥ 2 but < 3 ng / mL: return for PSA testing every 2 - 4 years
- PSA > 1 but < 2 ng / mL: continued screening every 2 - 4 or no further screening according to patient preference.
- PSA ≤ 1 ng / mL: no further screening

71 – 75:

- No screening for most men
- As for 60 - 70 for a subgroup of men in excellent health

76+:

- No further screening

Figure 1.

Table 1

Indications for biopsy in men with PSA ≥ 3 ng / mL.

The PSA level	Risk of aggressive prostate cancer continues to increase with PSA; a man with a PSA of 8–10 ng/mL commonly has higher risk of a clinically significant cancer than a man of the same age with a PSA of 3–4 ng/mL.
Results of the digital rectal exam (DRE)	Nodularity would clearly be an indication for biopsy; enlargement might suggest benign disease.
Age and comorbidities	Due to the strong association between age and overdiagnosis, there should be a greater propensity to biopsy men with longer life expectancy.
Race	African Americans have a higher risk of high grade disease than men of other races.
Changes in PSA	A recent sudden rise in PSA is often associated with benign disease.
Repeat PSA	Some men with elevated PSA will have PSA fall below biopsy thresholds on repeat PSA a few weeks later.
Reflex tests	Commercially available reflex tests – tests that are used if a first test is positive - that have been shown to be associated with the risk of high-grade disease include blood tests such as the free-to-total PSA ratio, the Prostate Health Index, the 4Kscore, and the urinary testing of PCA3.
Prior biopsy	A prior negative biopsy lowers the risk of aggressive disease.
Work-up and treatment of benign disease	Patients with symptoms of benign prostate disease, such as urinary urgency, are less likely to have prostate cancer for a given PSA level.
Use of 5-α reductase inhibitors	Interpretation of measured PSA level needs to take into account medications that affect PSA levels.
Patient preference	Some patients are more averse to invasive procedures, such as prostate biopsy, than others and so a higher overall risk of aggressive cancer might be required to indicate biopsy.