KAISER PERMANENTE

Prostate Cancer Screening Guideline

Last guideline approval: February 2013

Guidelines are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

Prevention

There is no conclusive evidence regarding alterations in lifestyle or diet for the prevention of prostate cancer.

Screening Recommendations

Helping men decide whether to be screened for prostate cancer

Before initiating or continuing prostate cancer screening, Kaiser Foundation Health Plan of Washington recommends that all men engage in explicit and informed decision making with their providers. Providers and patients should thoroughly review the limited benefits and significant harms of prostate cancer screening in the context of the patients' own values and preferences. (See Shared Decision Making, below, for key points and details about the harms and benefits of screening.)

Once the decision to screen is made, all positive results must be followed up and will likely lead to biopsy.

Men for whom screening is ***not*** recommended:

- Men aged less than 50 years (except those at higher risk)
- Men aged 70 years and older
- Men with a life expectancy of less than 10 years, as they are unlikely to benefit from screening

Prostate cancer screening ***may be considered*** for:

- Average-risk men aged 50–69 with a life expectancy greater than 10 years
- Black men aged 40–69
- Men aged 40–69 with one first-degree relative or two or more second-degree relatives diagnosed with prostate cancer before the age of 60

Shared Decision Making

Key points for shared decision making

- Prostate cancer screening was not found to have an overall survival benefit either in the American Prostate, Lung, Colorectal, and Ovarian (PLCO) screening study (Andriole 2012) or in the European Randomized Study of Screening for Prostate Cancer (ERSPC) (Schröder 2012).
- Based on the results of the ERSPC trial (Schröder 2012), to **prevent one death** from prostate cancer in 12 years:
  - **936 men** would need to be screened, and
  - **33 prostate cancers** would need to be detected.
- PSA screening cannot differentiate between indolent and lethal prostate cancer.

Direct harms of PSA screening

The accuracy of the PSA test depends on the cutoff value used. Lowering the PSA cutoff below 4.0 ng/mL might detect some aggressive cancers earlier, but would also increase the number of false positives, resulting in more referrals to Urology and potentially to unnecessary biopsies.

Positive test results lead to increased anxiety (Johansson 2011) and one or more biopsies, with their attendant risks:

Complications per 1,000 men undergoing biopsy (Raaijmakers 2002, Loeb 2011)

Hematospermia	504 in 1,000
Hematuria lasting longer than 3 days	226 in 1,000
Fever	35 in 1,000
Urinary retention	4 in 1,000
Hospitalization	5 in 1,000

Related harms of PSA screening

Of men who test positive for cancer using PSA, 90% will undergo early treatment with surgery, radiation, or androgen deprivation therapy (Moyer 2012).

Immediate harms from surgery (Moyer 2012)

Survival with serious post-surgical complications	10–70 in 1,000
Death within 1 month of surgery	5 in 1,000

Long-term harms from surgery or radiation (Moyer 2012). Please note that these risk numbers indicate the change in risk above baseline, not the total risk of urinary incontinence or erectile dysfunction for this population, which is significantly higher.

Urinary incontinence	200 in 1,000
Erectile dysfunction	300 in 1,000

Possible benefits of PSA screening

PSA screening may detect lethal cancers at an early stage.

Screening may reduce prostate cancer mortality in men aged 55–69 by 1.07 in 1,000 over 12 years (Schröder 2012).

Test Recommendations

After a fully informed shared decision making process, those men electing to undergo screening should have both a prostate-specific antigen (PSA) test **and** a digital rectal examination (DRE).

The use of PSA in conjunction with the DRE enhances early prostate cancer detection. The positive predictive value (PPV) is 31.5% for PSA alone, 21% for DRE alone, and 48.5% for PSA in conjunction with DRE (Catalona 1994).

PSA cutoffs

The accuracy of the PSA test depends on the cutoff value used. The literature indicates that there is no optimal PSA cutoff value that has simultaneously high sensitivity and specificity for detecting prostate cancer. The traditional cutoff for urology referral in centers around the world remains 4.0 ng/mL, although at this level PSA has a high specificity (90%) and a low sensitivity (20.5%). Lowering the PSA cutoff below 4.0 ng/mL might detect some aggressive cancers earlier, but would also increase the number of false positives, resulting in unnecessary biopsies.

Follow-up/Referral

Follow-up screening

For men with normal DRE **and** PSA less than or equal to 4.0 ng/mL, this guideline recommends repeat screening on the following schedule:

- For men with PSA **less than or equal to 2 ng/mL,** screen again with DRE and PSA in **2 years.**

- For men with PSA **greater than 2 ng/mL** but less than or equal to 4.0 ng/mL, screen again with DRE and PSA in **1 year.**

Referral criteria

This guideline recommends referral to Urology for men with an abnormal DRE **or** a PSA level above 4.0 ng/mL, or when clinical symptoms and physical exam warrant further evaluation.

Treatment Overview

Men found to have prostate cancer should engage in shared decision making about treatment options with their urologist. Management strategies for localized prostate cancer include active surveillance,* surgery, and radiation therapy. There is no consensus regarding optimal treatment strategies, but—given the potential harms of definitive treatment—Kaiser Foundation Health Plan of Washington recommends considering active surveillance by a urologist for patients at low to intermediate risk. Treatment should be individualized after considering the patient's life expectancy, disease characteristics, predicted outcomes, and preferences.

* *Active surveillance* or expectant management involves active monitoring of the disease through a formal regular process of biochemical tests and biopsies with the expectation to intervene if the cancer progresses. This approach is recommended for the management of men with low-risk disease who would potentially benefit from radical treatment.

Watchful waiting, on the other hand, is recommended for local disease when there are no clinical benefits of radical treatments, and is usually offered to older men and those with significant comorbidities.

Evidence Summary

The Prostate Cancer Screening Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

PSA screening

Screening may lead to early detection of some prostate cancers, but there is still no evidence to indicate that it improves health outcomes or prolongs life. The long-term results of both the American Prostate, Lung, Colorectal, and Ovarian (PLCO) screening study (Andriole 2012) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) did not show an overall survival benefit of screening for prostate cancer. However, the 11-year follow-up of the ERSPC trial (Schröder 2012) showed a statistically significant benefit of screening in reducing mortality from prostate cancer in a prespecified core group of men (aged 55–69 years); to prevent 1 death from prostate cancer in this group, the number needed to invite for screening (NNI) was 1,055, and the number needed to detect a cancer was 37. (NND) . The authors indicated that these NNI and NND varied largely according to the period of follow-up in all centers. Analysis of available data for at least 12 years of follow-up showed an NNI of 936 and an NND of 33.

PLCO and ERSPC were large trials with long-term follow-up, but both had their limitations:

The ERSPC trial was a combination of studies conducted in a number of European countries with different recruitment processes, eligibility criteria, randomization schemes, screening strategies, and follow-up. Each country followed its local diagnosis and treatment guidelines. The authors indicated that men in the screening arm who were diagnosed with prostate cancer were more likely than those in the control arm to be treated at academic centers. In addition, men with high-grade prostate cancer in the control arm were more likely to be treated with radiotherapy, expectant management, or hormonal treatment, while those in the screening arm were more likely to be treated with surgery. Causes of death were determined by committees whose members were blinded to study-group assignments but not to treatments. Misattribution of the cause of death might create a bias toward screening, since the diagnosis of more early-stage cancers in the ERSPC trial led to substantially more attempted curative treatments.

The PLCO study had a high contamination rate and may be viewed as a comparison of intensive or organized annual screening to less-intensive or opportunistic screening. It does not compare screening to no screening, and cannot determine whether screening reduces mortality. Because the PLCO only regarded men in the control arm as contaminants if they had more than two screenings in the 7–10 years of follow-up, over 50% of the PLCO control group were similar to the ERSPC screening group, who underwent screening every 4 or 7 years. In addition, a proportion of men already had an established baseline PSA, and thus some cancers detected at screening might have been eliminated before randomization.

Prostate cancer treatment improved during both the ERSPC and PLCO trials, which may have masked the effect of screening.

Benefits and harms of screening

Prostate cancer screening harms may be due to the screening process itself or to the diagnostic and treatment interventions based on the screening outcomes.

Direct harms of PSA testing and diagnostic interventions

The USPSTF found adequate evidence that the screening process produces at least small harms, including pain, fever, bleeding, infection, and transient urinary difficulties associated with prostate biopsy, as well as psychological effects of false-positive test results. Men who have a false-positive test result are more likely to have additional testing, including one or more biopsies in the following year (Moyer 2012).

The PLCO study results indicate that the complications resulting from the screening process were mild and infrequent. There were 0.3/10,000 events of bleeding or pain with the DRE exam, and 26.2/10,000 mild complications (dizziness, bruising and hematoma) with PSA testing. In the ERSPC study, 20% of the participants had at least one false-positive result, and after four PSA tests, men in

the screening group of the PLCO trial had a 12.9% cumulative risk for at least one false-positive result and 5.5% risk for at least one biopsy due to a false-positive result.

Harms of prostate biopsy reported by the Rotterdam center of the ERSPC trial (Raaijmakers 2002) include persistent hematospermia (50.4%), hematuria lasting more than 3 days (22.6%), fever (3.5%), urine retention (0.4%), and hospitalization for signs of prostatitis or urosepsis (0.5%).

Overdiagnosis/overtreatment
The USPSTF concluded that there is convincing evidence that PSA-based screening leads to substantial overdiagnosis of prostate tumors. Many men are subjected to the harms of treatment for prostate cancer that will never become symptomatic. Evidence indicates that 90% of men with PSA-detected prostate cancer in the United States have early treatment with surgery, radiation, or androgen deprivation therapy. Up to 5 in 1,000 men will die within 1 month of prostate cancer surgery and between 10 and 70 men will have serious complications but survive. Radiotherapy and surgery result in long-term adverse effects, including urinary incontinence and erectile dysfunction in at least 200–300 of 1,000 men treated with these therapies. Radiotherapy is also associated with bowel dysfunction (Moyer 2012).

Optimal age for screening

There is insufficient direct evidence to determine the optimal age at which prostate cancer screening should start or end.

Optimal PSA cutoff

The literature indicates that there is no optimal PSA test cutoff point that has simultaneously high sensitivity and specificity. The traditional cutoff for prostate biopsies in centers around the world remains 4.0 ng/mL. However, many practitioners are now using a cutoff in the range of 2.5–3.0 ng/mL before recommending a prostate biopsy.

At a cutoff of 4.0 ng/mL, the rate of false-positive results was 129 in 1,000 in the PLCO trial (Croswell 2009) and 125 in 1,000 in the Finnish center of the European ERSPC trial (Kilpeläinen 2010).

Using data from the Prostate Cancer Prevention Trial, Thompson and colleagues (2005) found that the sensitivity of serum PSA at 4.0 ng/mL is around 20% (missing over three-fourths of all biopsy-detectable cancers) and the specificity is around 93%. This cutoff correctly identified only 40.4% of cancers with a Gleason score $\geq$ 7. Lower cutoff values improved sensitivity at the expense of false-positive results (sensitivity at a 2.0 ng/mL cutoff is around 54% and specificity around 70%).

When age was considered, a cutoff of 4.1 ng/mL yielded a sensitivity of 27.7% and a specificity of 91.7% for men under 70 years, and 21.1% and 92.9% respectively for men aged 70 years or older.

Optimal screening interval

There is insufficient direct evidence to determine the optimal interval between screenings for prostate cancer. Different screening intervals have not been compared in randomized controlled trials (RCTs). The literature indicates that retesting intervals should be individualized according to the patient's initial PSA levels. There is indirect evidence that longer screening intervals might be appropriate for men with an initial PSA < 1.0 ng/mL.

Using data from the ERSPC trial, Roobol and colleagues (2007) compared the incidence of interval cancers (diagnosed during the screening interval but not detected by screening) between the men in the screening arms in the Gothenburg Swedish center (N = 4,202), who were screened for prostate cancer every 2 years, and the Rotterdam Dutch center (N = 13,301), who had a 4-year screening interval. The participants were 55–65 years of age at the initial screening. The 10-year cumulative incidence of all prostate cancers was 8.41% in Rotterdam versus 13.14% in Gothenburg ($p < .001$). However, the difference in the interval cancer between the two centers was statistically insignificant (0.43% vs. 0.745% respectively, $p = .51$). The difference between the two centers in the aggressive interval cancer was also insignificant. The authors concluded that the 2-year screening interval was associated with a higher

detection rate but not with lower rates of interval or aggressive interval prostate cancers. The analysis had several disadvantages that would limit generalization of the results. The participants were not randomized to the 2- and 4-year screening intervals, there were differences in protocol and patient characteristics between the two centers, and the authors did not relate the risk of aggressive interval cancer to the initial PSA level. Moreover, the results might not be applicable to populations of other ethnic origins.

In the Rotterdam part of the ERSPC study (Schröder 2008), men were re-screened at 4 and 8 years. The 8-year detection rate of prostate cancer among men with PSA < 1.0 ng/mL at baseline was 0.47%. In a comparison between round 1 and round 2 screening of the Rotterdam cohort, Postma and colleagues (2007) found a significant reduction in almost all prognostic factors between the first and second screening rounds. The detection rates were 5.1% at 4 years and an estimated 3% at 8 years. Locally extensive disease was reduced from 18.7% to 3.7%, the rate of Gleason scores $\geq$ 7 was reduced from 27% to 7%, and the proportion of minimal disease increased from 33% to 43%. These results indicate that overdiagnosis increases with repeat screening.

Crawford et al (2006) used data from the PLCO trial and statistical models to estimate the probability that a man with a baseline negative test (initial PSA $\leq$ 4.0 ng/mL) will have at least one positive test after a given period of annual testing. The cumulative probability of converting to positive PSA after 5 years was as follows:

Baseline PSA	Probability of PSA > 4.0 at 5 years (95% CI)
0 to < 1	1.5% (1.2–1.7%)
1 to < 2	7.4% (6.8–8.1%)
2 to < 3	33.5% (31.5–36%)
3 to 4	79% (77–81%)

Based on the results of their analysis, the investigators concluded that rescreening men with a baseline PSA < 1 ng/mL every 5 years, and men with a baseline PSA of 1–2 ng/mL every 2 years could result in a 50% reduction in PSA tests. They also concluded that rescreening on this schedule would result in < 1.5% of men potentially having a cancer diagnosed later than if they had been rescreened annually, but with an unknown effect on prostate cancer mortality.

PSA molecular forms and kinetics

PSA molecular forms and kinetics are not ready for use at this time. Studies on strategies to improve the performance of the PSA test in screening men for prostate cancer were focused on the different molecular forms of PSA in the serum, including free PSA (fPSA), complexed PSA (cPSA), and pro-PSA. Ratios and combinations of PSA tests, as well as PSA density, have also been studied. The studies do not provide sufficient evidence to determine whether the tests add to the clinical value of PSA testing.

Novel biomarkers for prostate cancer screening

A range of biologic and clinical measures are currently being investigated and validated in ongoing studies for their potential ability to predict the aggressive/high-grade tumors that will progress if left untreated. These include serum, tissue, or urine markers such as EPCA, EPCA-2, prostate cancer antigen 3 (PCA3), AMACR, methylated GSTP1, TMPRSS2-ETS gene rearrangement, DD3PCA3/UPM-3, and others.

The limited number and poor quality of published studies on novel prognostic markers, as well as the considerable variability in reported results, do not provide sufficient evidence to determine whether any of them have prognostic ability or can identify potentially aggressive or indolent disease.

Digital rectal examination (DRE)

The role of DRE in prostate cancer screening was examined in a number of cohort studies and substudies of RCTs. In a large prospective study, Catalona and colleagues (1994) compared the efficacy of DRE and PSA in the early detection of prostate cancer among 6,630 male volunteers from six university centers in the United States. All study participants underwent PSA testing either just before or at least 1 week after having a DRE performed by urological surgeons or medical oncologists experienced

in the examination of prostate cancer. TRUS guided needle quadrant biopsies were performed if the DRE was suspicious or if the PSA level was greater than 4.0 ng/mL. The results showed that the positive predictive values were 31.5% for PSA alone, 21% for DRE alone, and 48.5% for both combined.

A substudy of the Rotterdam cohort of ERSPC (Gosselaar 2008) investigated whether an abnormal DRE exam would add to the value of PSA $\geq$ 3.0 ng/mL as an indication for biopsy, and whether DRE has an additional effect in the identification of higher-grade prostate cancers (i.e., those with a Gleason score > 7). This substudy included 1,849 men 55–75 years of age (18% of those who underwent PSA testing) who had a baseline PSA level of $\geq$ 3.0 ng/mL and thus underwent a DRE and a TRUS-guided sextant biopsy. The results of the analysis showed that a suspicious DRE was associated with a higher chance of having prostate cancer: The positive predictive value (PPV) of an abnormal DRE in patients with PSA $\geq$ 3.0 ng/mL was almost twice that of a normal DRE in the initial screening (48.6% vs. 22.4%). Both PPVs decreased in screening round 2 (29.9% vs. 17.1%, respectively) and round 3 (21.2% vs. 18.2%, respectively). Of all prostate cancers with a Gleason score > 7, 71.0% were detected in men with a suspicious DRE ($p < 0.001$) in the initial screening round (68.8% in round 2, and 85.7 % in round 3).

Overall, the published literature indicates that:

- The positive predictive value and sensitivity of DRE are strongly dependent on PSA level.
- The specificity of DRE is high at all PSA levels.
- The detection rate and PPV of DRE improves with the addition of PSA and TRUS.
- Because DRE is a subjective test, its accuracy may vary according to the examiner, as well as the anatomic location and volume of the prostate examined.
- There is insufficient evidence to determine the impact of DRE screening on reducing prostate cancer mortality or preventing metastatic disease.

Treatment strategies

- There is insufficient evidence to determine whether treatment for early-stage prostate cancer detected by screening will improve survival.
- There is insufficient evidence to determine whether there is an optimal treatment or management strategy for prostate cancer cases detected by screening.
- There is also insufficient evidence to determine whether one treatment for localized prostate cancer is superior to other treatments or interventions, or is the right choice for all patients with PSA-detected prostate cancer.

The PIVOT trial (Wilt 2012) randomly assigned 731 men with localized prostate cancer (mean age, 67 years; median PSA value, 7.8 ng/mL) to radical prostatectomy or watchful waiting and followed them for a median of 10 years. The primary outcome was all-cause mortality, and the secondary outcome was prostate cancer mortality.

The long-term results of the PIVOT trial show statistically insignificant benefit for all-cause and prostate cancer mortality with radical prostatectomy versus watchful waiting. The incidence of bone metastases was, however, significantly lower in the patients assigned to the radical prostatectomy group, with a number needed to treat of 17 over 12 years. A subgroup analysis showed that radical prostatectomy was associated with a reduced all-cause mortality among men with a PSA value > 10 ng/mL. It is to be noted, however, that the study was initiated in 1994 and radical prostatectomy was compared to watchful waiting, not to active surveillance.

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Guideline Development Process and Team

Development process

The Prostate Cancer Screening Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

This edition of the guideline was approved for publication by the Guideline Oversight Group in February 2013.

Team

The Prostate Cancer Screening Guideline development team included representatives from the following specialties: clinical laboratory, family medicine, medical oncology, radiation oncology, and urology.

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