



Medical Coverage Policy

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Prostate-Specific Antigen (PSA) Screening for Prostate Cancer

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Overview

This Coverage Policy addresses prostate-specific antigen (PSA) testing for prostate cancer screening.

Coverage Policy

Prior to undergoing prostate-specific antigen (PSA) testing for prostate cancer screening an individual should make an informed decision after a discussion of the potential benefit and harm with his healthcare provider.

Annual PSA testing for prostate cancer screening is considered medically necessary for EITHER of the following:

- for asymptomatic men beginning at age 40 who are at high risk of prostate cancer because of **ANY** of the following:

- family history (i.e., multiple first-degree relatives diagnosed at an early age)
 - African-American race
 - previous borderline PSA levels
- for asymptomatic men beginning at age 45

Percent free PSA (%fPSA), free-to-total PSA ratio (fPSA/tPSA) testing and/or complexed PSA (cPSA) testing is considered medically necessary for determining the need for prostate biopsy in a man with a normal or equivocal digital rectal examination (DRE) and an elevated tPSA of 4–10 ng/mL.

%fPSA (or fPSA/tPSA) testing or cPSA testing as screening tests for asymptomatic men in the general population is considered experimental, investigational or unproven.

General Background

Prostate cancer is the most common cancer diagnosed in North American men, excluding skin cancers. It is estimated that in 2020, approximately 191,930 new cases and 33,320 prostate cancer–related deaths will occur in the United States. Prostate cancer is the second leading cause of cancer death in men, exceeded by lung cancer. Prostate cancer accounts for 21% of all male cancers and 10% of male cancer-related deaths (National Cancer Institute [NCI], 2020).

Incidence of prostate cancer increases with age: uncommon <50 years of age; 80% of new cases are diagnosed in patients aged ≥65 years. Widespread PSA testing has doubled the incidence of prostate cancer and the lifetime risk for prostate cancer to approximately 16%. Prostate cancer is diagnosed earlier, and the incidence of clinically “silent” T1 tumors has increased from 17% in 1989 to 48% in 2001 since the advent of PSA screening. Average age at time of diagnosis is 72 years. African Americans in the United States have the highest incidence of prostate cancer in the world (one in every nine males). Incidence of prostate cancer is low in Asians. Approximately 9% of all prostate cancers may be familial. Mortality rates of prostate cancer have declined substantially in the past 15 years from 34% in 1990 to <20% currently (Ferri’s Clinical Advisor, 2021). According to NCCN (2021), “men of African ancestry have a higher incidence of prostate cancer, increased prostate cancer mortality, and earlier age of diagnosis compared to Caucasian men. This is attributable to a greater risk of developing preclinical prostate cancer and a higher likelihood that a preclinical tumor will spread.”

Screening of asymptomatic men for prostate cancer has become a widespread practice in the United States. Test procedures used for prostate cancer screening include digital rectal examination (DRE) and prostate-specific antigen (PSA). Transrectal ultrasound (TRUS) is used for the evaluation of an abnormal DRE and/or abnormal PSA. The reference standard for these tests is pathologic confirmation of malignancy in tissue obtained by biopsy or surgical resection. While DRE is relatively noninvasive, its effectiveness is dependent on the skill and experience of the examiner. Although serum PSA and TRUS are more sensitive than DRE, increasing the diagnostic yield of prostate cancer when combined with rectal examination, these two tests are associated with high false-positive rates and may identify some tumors that will not threaten the patient’s health. It has been proposed that measurement of serum PSA may be a more promising screening test. The potential value of the PSA test appears to be its simplicity, objectivity, reproducibility, and lack of invasiveness. Thus, PSA is more commonly used as an adjunct to DRE (NCI, 2017/2020; Loeb, et al., 2016; U.S. Preventive Services Task Force [USPSTF], 2018).

PSA is a glycoprotein produced by both benign and malignant prostate epithelial tissue. Because a number of assays are commercially available, it is recommended that physicians use the same assay in following serial PSAs. Elevations can be seen after cystoscopy, acute urinary retention, prostate trauma (e.g., needle biopsy or prostatectomy), and with urinary tract or prostatic infection. DRE does not raise the PSA level; however, ejaculation may cause minor increases for a day or two. Benign prostatic hyperplasia (BPH) can also produce modest PSA elevations, and separating BPH from early prostate cancer is a major clinical problem with PSA screening (Barry, 2014). It is recommended that the interpretation of PSA values should always take into account

age, the presence of urinary tract infection or prostate disease, recent diagnostic procedures, and prostate-directed treatments (Loeb, et al., 2016).

The true sensitivity and specificity of PSA have been unclear because historically only men with elevated results underwent biopsy. Researchers have indirectly estimated that the sensitivity of PSA to detect cancers ultimately destined to present clinically at 50%—75%, with a specificity of about 90%; specificity deteriorates among older men or men with symptoms suggesting BPH. The predictive value of a PSA level greater than 4.0 ng/mL is about 30%, and is relatively insensitive to age because rising prevalence cancels the effect of decreasing specificity with age. The sensitivity of PSA relative to biopsy is only about 20% for all cancers and 40% for Gleason 7 or higher cancers at this traditional cut-point. Documentation of the relatively low sensitivity of PSA has prompted some experts to recommend biopsy at lower PSA levels, whereas others have been concerned that a lower biopsy threshold will produce too many negative biopsies as well as the overdiagnosis of many clinically unimportant cancers. Screening periodicity has not been established, but repeating the PSA measurement at 1- to 2-year intervals has been proposed (the longer interval might be used when the initial PSA level is <2.0 ng/mL; the shorter interval if the PSA is higher or if a more accurate estimate of PSA velocity is needed). The discovery of molecular derivatives of PSA, PCA3, new kallikrein markers, and gene rearrangements have been proposed to improve the efficiency of prostate cancer detection (Morgan, et al., 2016; Barry, 2014; Getzenberg, et al., 2011).

Normal PSA levels are not well-defined. In general, however, the higher a man's PSA level, the more likely it is that he has prostate cancer. Moreover, continuous rise in a man's PSA level over time may also be a sign of prostate cancer (NCI, 2017).

Recent textbook literature states that “measurement of PSA is controversial in early diagnosis of prostate cancer. PSA screening is associated with psychological harm, and its potential benefits remain uncertain. In asymptomatic men with no history of prostate cancer, screening using PSA does not reduce all-cause mortality or death from prostate cancer. Normal PSA is found in >20% of patients with prostate cancer, whereas only 20% of men with PSA levels between 4 ng/ml and 10 ng/ml have prostate cancer. Most guidelines encourage a shared decision-making approach between patient and physician regarding PSA testing. Available evidence favors clinician discussion of the pros and cons of PSA screening with average-risk men aged 65 to 69 yr. Only men who express a definite preference for screening should have PSA testing. Rather than widespread annual PSA screening, a reasonable approach may be to focus on high-risk men (those with PSA levels ≥ 2 ng/ml at age 60)” (Ferri's Clinical Advisor, 2021).

PSA Derivatives

Serum total PSA was the only PSA-based test available in early detection programs for prostate cancer. Since then, several PSA derivatives have been developed and proposed to improve the performance of the PSA measurement, thus possibly increasing specificity and decreasing unnecessary biopsies (National Comprehensive Cancer Network® [NCCN], 2021). These PSA derivatives include:

- **Percent free PSA (%fPSA) or free-to-total PSA ratio (fPSA/tPSA) versus complexed PSA (cPSA):** PSA circulates in the blood freely (fPSA) or bonded to a protein molecule (cPSA). Total PSA is the sum of the free and bound forms. This is what is measured as the standard PSA test. Unless otherwise noted, PSA means tPSA. Benign prostate conditions produce more fPSA, whereas cancer produces more of the cPSA. The free-to-total PSA ratio (fPSA/tPSA) may be a useful measure to be used as an adjunct to PSA testing. The fPSA and cPSA measurements are used when levels are between 4 and 10 ng/mL to decide whether a biopsy is needed (NCCN, 2021; Barry, 2014).
- **PSA velocity:** PSA velocity is used in younger men who begin early detection programs before age 50. PSA velocity is the rate of change in PSA levels over time. For men with PSA < 4 ng/mL, data suggest that a PSA velocity of ≥ 0.35 ng/mL is suspicious for the presence of cancer, and biopsy is recommended. For men with PSA 4–10 ng/mL, PSA velocity of ≥ 0.75 ng/mL is suspicious for cancer. PSA velocity in men with PSA > 10 ng/mL is not available. Current recommendations for the use of PSA velocity include collection of PSA levels over a period of no less than 18 months and the use of multiple values (i.e., minimum of three) to perform the calculation. In addition to the fact that multiple measurements using the same assay over a relatively long period of time are necessary for accuracy, there is substantial biologic and laboratory variability in PSA testing that may limit the accurate

interpretation of PSA velocity. PSA velocity provides a useful serial test for following up the millions of men with “normal” serum PSA levels that have made the decision to start early detection screening for prostate cancer (NCCN, 2021; Carter, et al., 2006).

- **PSA density (PSAD):** PSAD requires measurement of prostate volume by TRUS and is expressed as the PSA value (in nanograms per milliliter) divided by the prostate volume (in cubic centimeters). The lack of precision of measurement of both PSA and prostate volume has prevented the widespread clinical use of PSAD (NCCN, 2021).

U.S. Food and Drug Administration (FDA)

A number of different manufacturers make PSA test kits (FDA, 2021). The FDA approved the PSA test for use with the DRE to help detect prostate cancer in men age 50 or older and to monitor patients with a history of prostate cancer. The FDA indications for use of fPSA state the test is used along with a DRE and tPSA for men age 50 or older who have a PSA level between 4–10 ng/mL and a prostate gland that appears of normal size and texture (FDA, 2004).

Literature Review

There have been a number of clinical studies identified in the peer-reviewed medical literature that address the impact of PSA screening on the stage of cancer detection and on disease-specific survival rates, as well as studies that evaluate the relative sensitivities and specificities of derivative types of PSA testing. Although PSA testing is widely used there is controversy regarding the question of whether PSA-based screening reduces prostate cancer mortality. In addition, PSA-based screening is associated with risks of overdiagnosis and overtreatment. Results of two large, randomized studies illustrate this controversy—Andriole et al. (2005, 2009, 2012) reported on results of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and Schröder et al. (2009, 2012a, 2012b, 2014) who reported on the European Randomized Study of Screening for Prostate Cancer (ERSPC). Both studies are on-going with further follow-up and results expected in the future.

Randomized, Controlled Trials of Prostate-Specific Antigen-Based Screening: In a randomized study, Sandbloom et al. (2011) assessed whether screening for prostate cancer reduces prostate cancer specific mortality. The study included all men aged 50-69 in the city of Norrköping, Sweden, identified in 1987 in the National Population Register (n=9026). A total of 1494 men were randomly allocated to be screened by including every sixth man from a list of dates of birth. These men were invited to be screened every third year from 1987 to 1996. On the first two occasions screening was done by digital rectal examination only. From 1993, this was combined with prostate specific antigen testing, with 4 µg/L as cut off. On the fourth occasion (1996), only men aged 69 or under at the time of the investigation were invited. The main outcome measures were data on tumor stage, grade, and treatment from the South East Region Prostate Cancer Register and prostate cancer specific mortality up to December 31, 2008. In the four screenings from 1987-1996 attendance was 78%, 70%, 74%, and 74%, respectively. There were 85 cases (5.7%) of prostate cancer diagnosed in the screened group and 292 (3.9%) in the control group. The risk ratio for death from prostate cancer in the screening group was 1.16 (95% confidence interval 0.78-1.73). In a Cox proportional hazard analysis comparing prostate cancer specific survival in the control group with that in the screened group, the hazard ratio for death from prostate cancer was 1.23 (0.94 to 1.62; p=0.13). After adjustment for age at start of the study, the hazard ratio was 1.58 (1.06 to 2.36; p=0.024). The authors concluded that after 20 years of follow-up the rate of death from prostate cancer did not differ significantly between men in the screening group and those in the control group.

European Randomized Study of Screening for Prostate Cancer (ERSPC): The ERSPC is an ongoing randomized controlled study that was initiated in the early 1990s to evaluate the effect of screening with PSA testing on death rates from prostate cancer. The trial involved 182,000 men between the ages of 50 and 74 years through registries in seven European countries randomly assigned to a group that was offered PSA screening at an average of once every four years or to a control group that did not receive such screening. The predefined core age group for this study included 162,243 men between the ages of 55 and 69 years. The primary outcome was the rate of death from prostate cancer. In the screening group, 82% of men accepted at least one offer of screening. During a median follow-up of nine years, the cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. There were 214 prostate cancer deaths in the screening group, and 326 in the control group. The rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80 (95% confidence interval [CI], 0.65—0.98; adjusted p= 0.04). The researchers reported that PSA-based screening reduced the rate of death from prostate

cancer by 20%. They reported that this was associated with a high risk of over-diagnosis. Statistically, 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer (Schröder, et al., 2009).

Hugosson et al. (2019) reported 16 year prostate cancer (PCa) mortality outcomes of the ERSPC trial. The rate ratio of PCa mortality was 0.80 at 16 years. The difference in absolute PCa mortality increased from 0.14% at 13 years to 0.18% at 16 years. The number of men needed to be invited for screening to prevent one PCa death was 570 at 16 years compared with 742 at 13 years. The number needed to diagnose was reduced to 18 from 26 at 13 years. Men with PCa detected during the first round had a higher prevalence of PSA >20 ng/ml (9.9% compared with 4.1% in the second round, $p < 0.001$) and higher PCa mortality than those detected subsequently. This 16-yr report from ERSPC shows that the absolute effect of screening on PCa mortality increases with longer follow-up.

Schröder et al. (2012a) updated prostate cancer mortality in the ERSPC study. After a median follow-up of 11 years in the core age group, the relative reduction in the risk of death from prostate cancer in the screening group was 21% and 29% after adjustment for noncompliance. The absolute reduction in mortality in the screening group was 0.10 deaths per 1000 person-years or 1.07 deaths per 1000 men who underwent randomization. The rate ratio for death from prostate cancer during follow-up years 10 and 11 was 0.62. To prevent one death from prostate cancer at 11 years of follow-up, 1055 men would need to be invited for screening and 37 cancers would need to be detected. There was no significant between group difference in all-cause mortality. The authors reported that analyses after two additional years of follow-up consolidated their previous finding that PSA-based screening significantly reduced mortality from prostate cancer but did not affect all-cause mortality.

Schröder et al. (2014) updated prostate cancer mortality in the ERSPC study. The results are based on prostate cancer incidence and mortality truncated at 9, 11, and 13 years of follow-up in the intervention arm (offered PSA testing) relative to the control arm. For the first time, France is included in the analysis of prostate cancer incidence at 9 years of follow-up, but not of prostate cancer mortality because of incomplete follow-up to the end of 2010. The rate ratio (RR) of prostate cancer incidence between the intervention and control arms was 1.91 after 9 years (1.64 including France), 1.66 after 11 years and 1.57 after 13 years. The RR of prostate cancer mortality was 0.85, 0.78 and 0.79 at 9, 11 and 13 years respectively (95% confidence interval 13-year 0.69–0.91, $p = 0.001$). This corresponds to a relative risk reduction of 21% and an absolute risk reduction of death from prostate cancer at 13 years of 0.11 per 1,000 person-years or 1.28 per 1,000 men randomized, which is equivalent to one prostate cancer death averted per 781 men invited for screening or one per 27 additional prostate cancers detected. Prostate cancer mortality reduction in screened men after adjustment for non-participation was 27%. The author conclusions state that with data truncated at 13-years of follow-up, the present study continues to demonstrate a significant 21% relative prostate cancer mortality reduction in favor of screening, with one prostate cancer death averted per 781 men invited and 27 excess cases detected. The relative risk reduction in men actually screened was 27% after adjustment for selection effects. In spite of these findings further quantification of harms and their reduction are still considered as pre-requirements for the introduction of population based screening. The authors mention that hope lies in the further development of multi-parametric MRI imaging technology of the prostate.

In a randomized trial, Schröder et al. (2012b) assessed the effect of screening for prostate cancer on the incidence of metastatic disease. Data were available for 76,813 men aged 55-69 years coming from four centers of the ERSPC. The presence of metastatic disease was evaluated by imaging or by prostate-specific antigen (PSA) values >100 ng/ml at diagnosis and during follow-up. Regular screening based on serum PSA measurements was offered to 36270 men randomized to the screening arm, while no screening was provided to the 40543 men in the control arm. After a median follow-up of 12 years, 666 men with M+ prostate cancer were detected, 256 in the screening arm and 410 in the control arm, resulting in cumulative incidence of 0.67% and 0.86% per 1000 men, respectively ($p < 0.001$). This finding translated into a relative reduction of 30% (hazard ratio [HR]: 0.70; 95% confidence interval [CI], 0.60-0.82; $p = 0.001$) in the intention-to-screen analysis and a 42% ($p = 0.0001$) reduction for men who were actually screened. An absolute risk reduction of metastatic disease of 3.1 per 1000 men randomized (0.31%) was found. A large discrepancy was seen when comparing the rates of M+ detected at diagnosis and all M+ cases that emerged during the total follow-up period, a 50% reduction (HR:

0.50; 95% CI, 0.41-0.62) versus the 30% reduction. The reported limitation is incomplete explanation of the lack of an effect of screening during follow-up.

Kilpelainen et al. (2013) evaluated mortality results in the Finnish Prostate Cancer Screening Trial, the largest component of ERSPC. The primary endpoint was prostate cancer-specific mortality. A total of 80,144 men were identified from the population registry and randomized to either a screening arm (SA) or a control arm (CA). Men in the SA were invited to serum PSA determination up to three times with a 4-year interval between each scan and referred to biopsy if the PSA concentration was greater than or equal to 4.0 ng/mL or 3.0 to 3.99 ng/mL with a free/total PSA ratio less than or equal to 16%. Men in the CA received usual care. The analysis covers follow-up to 12 years from randomization for all men. PC incidence was 8.8 per 1000 person-years in the SA and 6.6 in the CA (HR=1.34, 95% confidence interval [CI]=1.27-1.40). The incidence of advanced prostate cancer was lower in the SA versus CA arm (1.2 versus 1.6, respectively; HR=0.73, 95% CI = 0.64-0.82; $p<0.001$). For prostate cancer mortality, no statistically significant difference was observed between the SA and CA (HR=0.85, 95% CI=0.69-1.04) (with intention-to-screen analysis). The authors reported that to avoid one prostate cancer death, you would need to invite 1199 men to screening and to detect 25 prostate cancers. There was no difference in all-cause mortality between trial arms. Reported limitations of this study are that there is no measure of the degree of contamination in the CA. Furthermore, if there was a bias in treatment modalities between the SA and CA, it would magnify rather than dilute the screening effect.

In a prospective study of the Finnish Prostate Cancer Screening Trial, Saarimäki et al. (2015) evaluated the impact of family history on outcomes of prostate cancer. PSA test performance (sensitivity and specificity) was slightly inferior for family history positives. No difference in prostate cancer mortality was observed in terms of family history.

In a cohort study, Loeb et al. (2012) examined the long-term outcomes of radical prostatectomy (RP) among men diagnosed with prostate cancer from the screening and control arms of the Rotterdam section of the ERSPC. Among 42,376 men randomized during the period of the first round of the trial (1993-1999), 1151 and 210 in the screening and control arms were diagnosed with prostate cancer, respectively. Of these men, 420 (36.5%) screen-detected and 54 (25.7%) controls underwent RP with long-term follow-up data (median follow-up 9.9 years). Progression-free (PFS), metastasis-free (MFS) and cancer-specific survival (CSS) rates were examined, and multivariable Cox proportional hazards models were used to determine whether screen-detected (versus control) was associated with RP outcomes after adjusting for standard predictors. RP cases from the screening and control arms had statistically similar clinical stage and biopsy Gleason score, although screen-detected cases had significantly lower prostate-specific antigen (PSA) levels at diagnosis. Men from the screening arm had a significantly higher PFS ($p=0.003$), MFS ($p<0.001$) and CSS ($p=0.048$). In multivariable models adjusting for age, PSA level, clinical stage, and biopsy Gleason score, the screening group had a significantly lower risk of biochemical recurrence (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.23-0.83, $P = 0.011$) and metastasis (HR 0.18, 95% CI 0.06-0.59, $P = 0.005$). Additionally adjusting for tumor volume and other RP pathology features, there was no longer a significant difference in biochemical recurrence between the screening and control arms. Limitations of the study include lead-time bias and non-randomized treatment selection.

Hugosson et al. (2010) reported findings from Göteborg in Sweden, one of the participating countries in the ERSPC trial (data from participants born between 1930 and 1939 were included in the pooled ERSPC data). The trial was designed and initiated independently from the ERSPC, although it was subsequently agreed to include a subset of participants in the ERSPC. A total of 20,000 men aged 50-64 years were randomized to PSA screening or a control group not offered screening; screening was every two years, and the PSA biopsy threshold was 3.4 ng/ml between 1995 and 1998, 2.9 ng/ml in 1999 and 2.5 ng/dL thereafter. Median follow-up was 14 years (complete for 78% of men). As with the larger ERSPC trial, more prostate cancers were diagnosed in the screening arm than in the control arm (11.4% of those screened versus 7.2% of controls). The authors report a statistically significant relative reduction in prostate cancer deaths (rate ratio, 0.56; 95% CI, 0.39-0.82; $p=0.002$). Overall, there were 44 prostate cancer deaths in the screened group (0.44%) versus 78 deaths in the control group (0.78%)—an absolute risk reduction of 0.34%. Thus, to avert one prostate cancer death, the corresponding number that would need to be invited to be screened would be 293, and the number who would need to be diagnosed and potentially treated (some men chose active surveillance) would be 12. No difference in overall mortality rates between the screened and control arms was found. The authors reported that PSA

screening is associated with a long and varying lead time, resulting in a risk of over-diagnosis that is substantial but still of a largely unknown magnitude.

Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (PLCO): The NCI is sponsoring a large RCT, the PLCO trial, to determine whether screening with PSA and DRE will reduce prostate cancer mortality. The initial round of screening is complete and has been reported by Andriole et al. (2005). The authors reported on the population enrolled in the trial, their baseline PSA and DRE screening results, and diagnostic results during the first year of follow-up. A total of 38,350 men were randomly assigned to the screening arm of the trial from November 1993 through June 2001. Men were advised to seek diagnostic follow-up from their primary physician if their DRE was suspicious for cancer and/or if their serum PSA level was higher than 4 ng/mL. Compliance with both screening tests was more than 89%. At screening, 7.5% of the men had a positive DRE, and 7.9% had a PSA level higher than 4.5 ng/mL. Of the men with positive screening tests, 74.2% had additional diagnostic testing, and 31.5% had a prostatic biopsy within one year. Of the men in the screening arm, 1.4% were diagnosed with prostate cancer, with the majority having clinically localized cancer. The compliance, biopsy, and cancer detection rates appear to be representative of the present practice patterns. However, the authors conclude that whether such screening will result in a reduction of prostatic cancer mortality will not be answered until the randomized comparison is completed.

Additional results from the PLCO trial showed that annual PSA testing for six years and annual DRE testing for four years (performed in the same years as the first four PSA tests) did not reduce the number of deaths from prostate cancer through a median follow-up period of 11.5 years (range 7.2–14.8 years). At seven years of follow-up, a point in time when follow-up of the participants was essentially complete, 23% more cancers had been diagnosed in the screening group than in the control group. In the control group, men were randomly assigned to “usual care.” These results suggest that many men were diagnosed with, and treated for, cancers that would not have been detected in their lifetime without screening and, as a consequence, were exposed to the potential harms of unnecessary treatments, such as surgery and radiation therapy. Nevertheless, it remains possible that a small benefit from the earlier detection of these “excess” cancers could emerge with longer follow-up. Follow-up of the PLCO participants will continue, therefore, until all participants have been followed for at least 13 years (Andriole, et al., 2009). After 13 years of follow-up, the cumulative mortality rates from prostate cancer in the intervention and control arms were 3.7 and 3.4 deaths per 10,000 person-years, respectively, resulting in a non-statistically significant difference between the two arms. The authors reported that after 13 years of follow-up, there was no evidence of a mortality benefit for organized annual screening in the PLCO trial compared with opportunistic screening, which forms part of usual care, and there was no apparent interaction with age, baseline comorbidity, or pretrial PSA testing (Andriole, et al., 2012).

Pinsky et al. (2012) analyzed prostate cancer specific survival in PLCO and its relation to screening. A total of 76,693 men aged 55-74 were randomized to usual care (n=38,350) or intervention (n=38,343). Intervention arm men received annual prostate-specific antigen (six years) and digital rectal exam (four years). Men were followed for cancer diagnosis and mortality through 13 years. Medical record abstractors confirmed prostate cancer diagnoses, stage and grade. There was no significant difference in prostate-specific survival rates between arms; 10 year survival rates were 94.7% (intervention, n=4250 cases) versus 93.5% (usual care, n=3815 cases). Within the intervention arm, cases never screened in PLCO had lower 10 year survival rates (82%) than screen detected or interval (following a negative screen) cases, both around 95.5%. The ratio of observed to expected 10 year prostate-specific death (1-survival) rates was 0.59 (95% CI: 0.51-0.68) for all PLCO cases, 0.66 (95% CI: 0.51-0.81) for Gleason 5-7 cases and 1.07 (95% CI: 0.87-1.3) for Gleason 8-10 cases. The authors report how much of the better survival is due to a healthy volunteer effect and to lead-time and overdiagnosis biases is not readily determinable. Pinsky et al. (2017) concluded that extended follow-up of the PLCO trial over a median of 15 years continues to indicate no reduction in prostate cancer mortality for the intervention compared to control arms. Due to the high rate of control arm PSA testing, the findings can be viewed as showing no benefit of organized over opportunistic screening.

Crawford et al. (2006) analyzed data from the PLCO Cancer Screening Trial. The objective of the study was to determine the risk, in men with normal baseline PSA, of converting to an abnormal (i.e., more than 4 ng/mL) PSA during a five-year period of subsequent annual PSA testing. Only 1.5% of men with initial baseline PSA of < 1 ng/mL converted to abnormal PSA after five years. The corresponding rates for men with initial PSA of 1–2, 2–3 and 3–4 were 7.4%, 33.5% and 79%, respectively. Of men with baseline PSA < than 1 ng/mL converting to a

PSA of more than 4 ng/mL, 8% were diagnosed with cancer within two years of conversion. Approximately 10% of men with baseline PSA < 1 ng/mL and negative baseline DRE had a positive DRE within three years. The authors reported that, "For men choosing PSA screening, screening every five years for baseline PSA < than 1 ng/mL and every two years for PSA 1–2 ng/mL, could result in a 50% reduction in PSA tests and in less than 1.5% of men missing earlier positive screens, but with an unknown effect on prostate cancer mortality."

Additional Trials of Prostate-Specific Antigen-Based Screening: Lilja et al. (2011) previously reported that a single prostate-specific antigen (PSA) measured at ages 44-50 was highly predictive of subsequent prostate cancer diagnosis in an unscreened population. The authors have reported an additional seven years of follow-up. This provides replication using an independent data set and allows estimates of the association between early PSA and subsequent advanced cancer (clinical stage >T3 or metastases at diagnosis). In this retrospective study, blood was collected from 21,277 men in a Swedish city (74% participation rate) during 1974-1986 at ages 33-50. Through 2006, prostate cancer was diagnosed in 1408 participants; PSA was measured in archived plasma for 1312 of these cases (93%) and for 3728 controls. At a median follow-up of 23 years, baseline PSA was strongly associated with subsequent prostate cancer (area under the curve, 0.72; 95% CI, 0.70-0.74; for advanced cancer, 0.75; 95% CI, 0.72-0.78). Associations between PSA and prostate cancer were virtually identical for the initial and replication data sets, with 81% of advanced cases (95% CI, 77%-86%) found in men with PSA above the median (0.63 ng/mL at ages 44-50). The authors reported that a single PSA at or before age 50 predicts advanced prostate cancer diagnosed up to 30 years later. Use of early PSA to stratify risk would allow a large group of low-risk men to be screened less often but increase frequency of testing on a more limited number of high-risk men. A reported limitation of this study is that the authors examined cancer diagnosis, rather than morbidity or mortality from cancer.

Relatively little is known about the risk profile and factors associated with treatment of prostate cancer in men whose PSA level is lower than 4ng/mL. In a retrospective study, Shao et al. (2010) used 2004-2006 data from the Surveillance, Epidemiology, and End Results (SEER) database, which contains the first available population-based collection of PSA levels and Gleason scores, to describe the risk profiles and treatment patterns of patients with prostate cancer and PSA levels below 4 ng/mL at the time of diagnosis. The study included records of 123,934 men over the age of 25 who had newly diagnosed prostate cancer. About 14 % of the men had PSA values lower than 4, generally younger men. In that group, 54 % had low-risk disease that could be safely monitored for progression with little risk. Nonetheless, 75 % of them received aggressive treatment, including a radical prostatectomy and radiation therapy. Among men in that group over the age of 65, in which "watchful waiting" is generally advised for low-risk disease, 66 % had aggressive therapy. Despite their lower risk of having clinically significant disease, treatment rates for men with PSA values of 4.0 ng/mL or lower were comparable to those of men presenting with PSA values between 4.0 and 20.0 ng/mL. The finding that men in low-risk groups were treated intensively raises the concern of overtreatment, especially among older patients.

In a cohort study, Roobol et al. (2007) attempted to determine how PSA screening affects prostate cancer mortality by comparing the number and characteristics of interval cancers, defined as those diagnosed during the screening interval but not detected by screening. The population studied were men in the screening arm of the ongoing European Randomized Study of Screening for Prostate Cancer (ERSPC) who were aged 55–65 years at the time of the first screening and were participating through two centers of the ERSPC: Gothenburg (two-year screening interval, n=4202) and Rotterdam (four-year screening interval, n=13,301). All participants who were diagnosed with prostate cancer through December 31, 2005, but at most 10 years after the initial screening were ascertained by linkage with the national cancer registries. A potentially life-threatening or aggressive interval cancer was defined as one with at least one of the following characteristics at diagnosis: stage M1 or N1, plasma PSA concentration > 20.0 ng/mL, or Gleason score > 7. The 10-year cumulative incidence of all prostate cancers in Rotterdam versus Gothenburg was 1118 (8.41%) versus 552 (13.14%) (p<0.001), the cumulative incidence of interval cancer was 57 (0.43%) versus 31 (0.74%) (p=0.51), and the cumulative incidence of aggressive interval cancer was 15 (0.11%) versus 5 (0.12%) (p=0.72). The rate of interval cancer, especially aggressive interval cancer, was low in this study. The authors reported that the two-year screening interval had higher detection rates than the four-year interval but did not lead to lower rates of interval and aggressive interval prostate cancers. The authors stated that the results of this study suggest "it does not seem justified to recommend annual PSA testing except in men at high risk of prostate cancer, who may be identifiable at secondary screening using recently developed algorithms" (Roobol, et al., 2007).

Systematic Review and Meta-Analysis Evaluating PSA Screening for Prostate Cancer: Wallner et al. (2013) conducted a systematic literature review to identify case control studies from the past 20 years that focused on evaluating the association between screening for prostate cancer and prostate cancer mortality. Emphasis was put on synthesizing the results of these studies, evaluating their limitations, and identifying remaining questions and issues that should be addressed in future studies. Seven studies were identified with the majority suggesting that a reduction in prostate cancer mortality is associated with PSA screening. However, the findings may be limited by various biases inherent to case control studies of screening tests, such as selection biases resulting from both case and control subject selection, exposure measurement issues, lead and length biases, and issues specific to prostate cancer screening such as the influence of digital rectal examinations. The authors concluded that findings from existing case control studies of PSA and prostate cancer mortality suggest that there is a mortality benefit from PSA screening. However, these studies may be limited by bias and must therefore be interpreted with caution. As uncertainty regarding PSA screening remains, future studies to evaluate the association between PSA and prostate cancer mortality should address these potential biases directly.

Djulebegovic et al. (2010) conducted a systematic review and meta-analysis to examine the evidence on the benefits and harms of screening for prostate cancer. Included studies were randomized controlled trials comparing screening by PSA with or without DRE versus no screening. Six randomized controlled trials from January 2005 to July 2010 with a total of 387,286 participants that met inclusion criteria were analyzed. The authors reported that all trials had one or more substantial methodological limitations. None of the studies provided data on the effects of screening on participants' quality of life. Minimal information was provided about potential harms associated with screening. The authors reported that the existing evidence from randomized controlled trials does not support the routine use of screening for prostate cancer with PSA with or without DRE.

Ilic et al. (2011) conducted an update to their 2006 Cochrane review to determine whether screening for prostate cancer reduces prostate cancer mortality and has an impact on quality of life. All RCTs of screening versus no screening or routine care for prostate cancer were eligible for inclusion in this review. Five RCTs with a total of 341,351 participants were included in this updated Cochrane systematic review. All involved PSA testing, although the interval and threshold for further evaluation varied across trials. The age of participants was 50–74 years, with durations of patient follow-up of 7–15 years. The methodological quality of three of the studies was assessed as posing a high risk of bias. Meta-analysis of the five included studies indicated no statistically significant difference in prostate cancer-specific mortality between men randomized to screening and control [relative risk (RR) 0.95, 95% CI 0.85–1.07]. Sub-group analyses indicated that prostate cancer specific mortality was not affected by age at which participants were screened. A preplanned analysis of a 'core' age group of men aged 55–69 years from the largest RCT (European Randomized Study of Screening for Prostate Cancer) reported a significant 20% relative reduction in prostate cancer specific mortality; (95% CI 0.65–0.98; absolute risk 0.71 per 1000 men). The number of men diagnosed with prostate cancer was significantly greater in men randomized to screening, compared with those randomized to control (RR 1.35, 95% CI 1.06–1.72). Harms of screening included high rates of false-positive results for the PSA test, over-diagnosis and adverse events associated with transrectal ultrasonography guided biopsies such as infection, bleeding and pain. The authors concluded that prostate cancer screening did not significantly decrease all-cause or prostate cancer-specific mortality in a combined meta-analysis of five RCTs. Any benefits from prostate cancer screening may take > 10 years to accrue; therefore, men who have a life expectancy of < 10–15 years should be informed that screening for prostate cancer is not beneficial and has harms. The authors reported that while the PSA test may be prostate specific, it is not specific to prostate cancer; therefore, continued research into alternative prostate-specific markers is required. A 2013 update to this Cochrane review reached similar conclusions (Ilic, et al., 2013).

Clinical Studies Evaluating the Utility of Additional PSA Derivatives: There is substantial evidence that use of the PSA parameters, %fPSA (or fPSA/tPSA) and cPSA, has the potential to decrease the number of unnecessary biopsies in men with a tPSA between 4 and 10 ng/mL, enhancing the performance of the PSA test. However, as is the case with PSA testing, it has not yet been proven that %fPSA testing or cPSA testing can alter the long-term clinical outcome of men with prostate cancer (Lee, et al., 2006; Roddam, et al., 2005 ; Hugosson, et al., 2003; Horninger, et al., 2002 ; Gann, et al., 2002; Djavan, et al., 2002; Roehl, et al., 2002; Brawer, et al., 2000/2002; Mitchell, et al., 2001).

Professional Societies/Organizations

National Comprehensive Cancer Network® (NCCN®): The 2021 National Comprehensive Cancer Network Guideline™ (NCCN Guideline™) on Prostate Cancer Early Detection states in the NCCN Recommendations that factors to consider in the early detection of prostate cancer include the patient's age, life expectancy, race, presence of inherited mutations, family history, and previous results from early detection tests.

The NCCN Panel recommends that baseline testing should be offered to healthy, well-informed men aged 45 to 75 years based on the results of RCTs. Baseline testing may be complemented by DRE. The panel recommends frequency of testing be 2 to 4 years for men aged 45 to 75 years with serum PSA values below 1 ng/mL. For men with PSA of 1 to 3 ng/mL, testing should occur at 1 to 2 year intervals. The panel recommends that PSA testing be considered only in very select patients after the age of 75 years (category 2B [Based on lower-level evidence, there is NCCN consensus that the intervention is appropriate]) and that indication for biopsy be carefully evaluated. Panel members uniformly discourage PSA testing in men unlikely to benefit from prostate cancer diagnosis based on age and/or comorbidity (NCCN, 2021).

The NCCN reported on the limitations of the randomized controlled trials stating that they do not address the potential benefit of screening in men with high-risk factors. Less than 5% of PLCO participants were of African-American descent and only 7% reported a family history of prostate cancer. Many men in the studies underwent sextant prostate biopsies rather than extended core biopsies, the standard diagnostic technique used today. The ERSPC may have underestimated benefit due to advanced age at first PSA test (median above 60), the low intensity of screening (largely every four years), and possible suboptimal treatment available in Europe in the 1990s compared to treatment that is available today (NCCN, 2021).

U.S. Preventive Services Task Force (USPSTF): The USPSTF 2018 updated recommendations for prostate cancer screening state, "For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)-based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening". The USPSTF assigned a Grade C recommendation which is defined as "The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small". The suggestions for practice state "offer or provide this service for selected patients depending on individual circumstances." The USPSTF reported that the new evidence that led to the change from a D to a C grade included longer-term follow-up of the ERSPC trial and new data on reductions in risk of metastatic disease with screening. Although the added benefit reported from the additional follow-up to 13 years (from 10 years) in the ERSPC trial increased the number of lives saved from 1.07 to 1.28 (a small amount, according to some comments), these results gave the USPSTF more confidence that the benefit of screening could be greater over a 20- to 30-year period. The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older (Grade D) (USPSTF 2018).

American Academy of Family Physicians (AAFP): The AAFP recommendations are adapted from the Final Recommendation Statement: Prostate Cancer: Screening from the U.S. Preventive Task Force. May 2018.

(ACP): The ACP published a Guidance Statement on Prostate Cancer Screening (Qaseem, et al., 2013). This guidance statement is derived from an appraisal of available guidelines on screening for prostate cancer. The authors selected four guidelines developed by the American College of Preventive Medicine (Lim, et al., 2008), American Cancer Society (Wolf, et al., 2010), American Urological Association (Greene, et al., 2009), and U.S. Preventive Services Task Force (2008). Guidance Statement 1 recommends, "that clinicians inform men between the age of 50 and 69 years about the limited potential benefits and substantial harms of screening for prostate cancer. ACP recommends that clinicians base the decision to screen for prostate cancer using the prostate-specific antigen test on the risk for prostate cancer, a discussion of the benefits and harms of screening,

the patient's general health and life expectancy, and patient preferences. ACP recommends that clinicians should not screen for prostate cancer using the prostate-specific antigen test in patients who do not express a clear preference for screening. Guidance Statement 2: ACP recommends that clinicians should not screen for prostate cancer using the prostate-specific antigen test in average-risk men under the age of 50 years, men over the age of 69 years, or men with a life expectancy of less than 10 to 15 years. Prostate cancer screening with the PSA test is controversial". There has been no update to this guidance statement since 2013.

American Cancer Society (ACS): The ACS guideline for the early detection of prostate cancer recommends that asymptomatic men who have at least a 10-year life expectancy have an opportunity to make an informed decision with their health care provider about screening for prostate cancer after they receive information about the uncertainties, risks, and potential benefits associated with prostate cancer screening. Prostate cancer screening should not occur without an informed decision-making process. Men at average risk should receive this information beginning at age 50 years. Men in higher risk groups should receive this information before age 50 years. Men should either receive this information directly from their health care providers or be referred to reliable and culturally appropriate sources. Patient decision aids are helpful in preparing men to make a decision whether to be tested. Men at higher risk, including African American men and men who have a first-degree relative (father or brother) diagnosed with prostate cancer before age 65 years, should receive this information beginning at age 45 years. Men at appreciably higher risk (multiple family members diagnosed with prostate cancer at an early age) should receive this information beginning at age 40 years (ACS, 2020).

National Cancer Institute (NCI): The NCI summary of evidence for prostate cancer screening addressing benefits states, "The evidence is insufficient to determine whether screening for prostate cancer with prostate-specific antigen (PSA) or digital rectal exam (DRE) reduces mortality from prostate cancer. Screening tests are able to detect prostate cancer at an early stage, but it is not clear whether this earlier detection and consequent earlier treatment leads to any change in the natural history and outcome of the disease. Observational evidence shows a trend toward lower mortality for prostate cancer in some countries, but the relationship between these trends and intensity of screening is not clear, and associations with screening patterns are inconsistent. The observed trends may be due to screening or to other factors such as improved treatment. Results from two randomized trials are inconsistent". The summary of evidence for harms states that "based on solid evidence, screening with PSA and/or DRE results in overdiagnosis of prostate cancers, and detection of some prostate cancers that would never have caused important clinical problems. Thus, screening leads to some degree of overtreatment. Based on solid evidence, current prostate cancer treatments, including radical prostatectomy and radiation therapy, result in permanent side effects in many men. The most common of these side effects are erectile dysfunction and urinary incontinence. Screening also leads to false-positive findings, with sequelae involving unnecessary diagnostic procedures. In addition, the screening process itself can lead to adverse psychological effects in men who have a prostate biopsy but do not have identified prostate cancer. Prostatic biopsies are associated with complications, including fever, pain, hematospermia/hematuria, positive urine cultures, and rarely sepsis" (NCI, 2019).

American Urological Association (AUA): In 2013, the AUA published a new Clinical Guideline on the Early Detection of Prostate Cancer (reviewed and validity confirmed in 2018; AUA, 2018). The guideline, which addresses screening in asymptomatic men of average risk of prostate cancer, updates the Association's Best Practice Statement on Prostate-Specific Antigen (PSA), originally released in 2009 (Carter, et al., 2013). The guidelines do not apply to symptomatic men or those at high risk for disease (men with a family history or of African-American race), who are encouraged to discuss their individual case with their doctor, regardless of their age. The AUA commissioned an independent group to conduct a systematic review and meta-analysis of the published literature on prostate cancer detection and screening. When sufficient evidence existed, the body of evidence for a particular intervention was assigned a strength rating of A (high), B (moderate) or C (low).

- "The Panel recommends against PSA screening in men under age 40 years. (Recommendation; Evidence Strength Grade C) In this age group there is a low prevalence of clinically detectable prostate cancer, no evidence demonstrating benefit of screening and likely the same harms of screening as in other age groups.
- The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (Recommendation; Evidence Strength Grade C) For men younger than age 55 years at higher risk (e.g.

positive family history or African American race), decisions regarding prostate cancer screening should be individualized.

- For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of preventing prostate cancer mortality in 1 man for every 1,000 men screened over a decade against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences. (Standard; Evidence Strength Grade B). The greatest benefit of screening appears to be in men ages 55 to 69 years.
- To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening. As compared to annual screening, it is expected that screening intervals of two years preserve the majority of the benefits and reduce overdiagnosis and false positives. (Option; Evidence Strength Grade C) Additionally, intervals for rescreening can be individualized by a baseline PSA level.
- The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy. (Recommendation; Evidence Strength Grade C) Some men age 70+ years who are in excellent health may benefit from prostate cancer screening."

American College of Preventive Medicine (ACPM): In 2008, the American College of Preventive Medicine (ACPM) updated their 1998 position statement on prostate cancer screening concluding that "there is insufficient evidence to recommend routine population screening with DRE or PSA. Clinicians caring for men, especially African-American men and those with positive family histories, should provide information about potential benefits and risks of prostate cancer screening, and the limitations of current evidence for screening, in order to maximize informed decision making." The ACPM recommendations state that "pending resolution of ongoing controversies, screening for prostate cancer among African-American men and those with a family history of prostate cancer has the potential to detect treatable forms of disease that are more likely to occur in these groups than in the general population. While the usual age for prostate cancer screening is between 50–70 years in average risk men, it has been suggested that those who are at high risk may benefit from earlier screening beginning at age 45, while higher-risk men (i.e., those with two or more first-degree relatives with prostate cancer before age 65) be screened at age 40" (Lim, et al., 2008). This statement has not been updated since 2008.

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative: The following recommendations for PSA screening for prostate cancer include:

- American Urological Association: Offer PSA screening for detecting prostate cancer only after engaging in shared decision making (2015).
- American Society of Clinical Oncology: Don't perform PSA testing for prostate cancer screening in men with no symptoms of the disease when they are expected to live less than 10 years (2013).
- American Academy of Family Physicians: Do not routinely screen for prostate cancer using a prostate-specific antigen (PSA) test or digital rectal exam. For men who desire PSA screening, it should only be performed after engaging in shared decision making (2018).
- American College of Preventive Medicine: Don't routinely perform PSA-based screening for prostate cancer (2015).

Use Outside of the US

European Society for Medical Oncology (ESMO): The 2015 ESMO Prostate Cancer Clinical Practice Guidelines (Parker et al., 2015) for diagnosis, treatment and follow-up addresses recommendations for incidence and mortality and diagnosis for prostate cancer. Levels of evidence and grades of recommendation are described as follows:

Levels of evidence:

- I Evidence from at least one large, randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
- II Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity

- III Prospective cohort studies
- IV Retrospective cohort studies or case–control studies
- V Studies without control group, case reports, experts opinions

Grades of recommendation:

- A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
- B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
- C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,...), optional
- D Moderate evidence against efficacy or for adverse outcome, generally not recommended
- E Strong evidence against efficacy or for adverse outcome, never recommended

The recommendations for screening and early detection state that:

- Population-based screening for prostate cancer reduces prostate cancer mortality at the expense of over diagnosis and overtreatment and is not recommended [I,C].
- Testing for prostate cancer in asymptomatic men should not be done in men over the age of 70 years [I, B].

The recommendations for diagnosis and pathology state that:

- A single elevated PSA level should not prompt a prostate biopsy, and should be verified by a second value [IV, B].
- The decision whether or not to have a prostate biopsy should be made in the light of DRE findings, ethnicity, age, co-morbidities, PSA values, free/total (f/t) PSA, history of previous biopsy and patient values [II, B].
- Transrectal ultrasound-guided prostate biopsy should be carried out under antibiotic cover and local anaesthesia, and a minimum of 10–12 cores obtained [II, B].
- Before repeat biopsy, multi-parametric MRI is recommended with a view to MRI-guided or MRI-transrectal ultrasound (TRUS) fusion biopsy [III, B].

European Association of Urology (EAU): The updated 2019 EAU, European Society for Radiotherapy & Oncology (ESTRO), European Society of Urogenital Radiology (ESUR) and the European Association of Nuclear Medicine (EANM) Guidelines on screening, diagnosis, and local treatment with curative intent of clinically localized prostate cancer guidelines for screening and early detection recommendations state:

- Do not subject men to PSA testing without counselling them about the potential risks and benefits (Level of evidence [LE] 3: Strength rating [SR] strong).
- Offer an individualized risk-adapted strategy for early detection to a well-informed man with a good performance status and a life expectancy of at least 10–15 yr (LE 3: SR strong).
- Offer early PSA testing in well-informed men at elevated risk of having prostate cancer (PCa):
 - Men aged >50 yr;
 - Men aged >45 yr and a family history of PCa;
 - African American men aged >45 yr. (LE 2b: SR strong).
- Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two years for those initially at risk:
 - Men with a PSA level >1 ng/ml at age 40 yr
 - Men with a PSA level >2 ng/ml at age 60 yr
 Postpone follow-up to eight years in those not at risk (LE 3: SR weak).
- Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life expectancy <15 years are unlikely to benefit (LE 3: SR strong).

Canadian Task Force on Preventive Health Care: The 2014 Canadian Task Force on Preventive Health Care recommendations on screening for prostate cancer with the prostate-specific antigen test updates the 1994 recommendations. The recommendations apply to all men without a previous diagnosis of prostate cancer. Strong recommendations are those for which the task force is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable

effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). A strong recommendation implies that most individuals will be best served by the recommended course of action.

Weak recommendations are those for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or the undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists. A weak recommendation implies that most men would want the recommended course of action but that many would not. For clinicians, this means they must recognize that different choices will be appropriate for each person, and they must help each patient arrive at a management decision consistent with his values and preferences. Policy-making will require substantial debate and involvement of various stakeholders. Weak recommendations result when the balance between desirable and undesirable effects is small, the quality of evidence is lower, or there is more variability in the values and preferences of patients.

The quality of evidence is graded as high, moderate, low or very low, based on how likely further research is to change our confidence in the estimate of effect.

The 2014 recommendations include:

- For men aged less than 55 years, we recommend not screening for prostate cancer with the prostate-specific antigen (PSA) test. (Strong recommendation; low-quality evidence.)
- For men aged 55–69 years, we recommend not screening for prostate cancer with the PSA test. (Weak recommendation; moderate-quality evidence.)
- For men 70 years of age and older, we recommend not screening for prostate cancer with the PSA test. (Strong recommendation; low-quality evidence.)
-

Canadian Urological Association (CUA): The 2017 CUA guideline (Rendon, et al., 2017) on recommendations on prostate cancer screening and early diagnosis states:

- Offer PSA screening to men with a life expectancy greater than 10 years. The decision of whether or not to pursue PSA screening should be based on shared decision-making after the potential benefits and harms associated with screening have been discussed (Level of evidence: 1; Grade of recommendation: B).
- For men electing to undergo PSA screening, we suggest starting PSA testing at age 50 in most men and at age 45 in men at an increased risk of prostate cancer (Level of evidence: 3; Grade of recommendation: C).
- For men electing to undergo PSA screening, we suggest that the intervals between testing should be individualized based on previous PSA levels.
 - For men with PSA 3 ng/ml, consider more frequent PSA testing intervals or adjunctive testing strategies (Level of evidence: 4; Grade of recommendation: C).
 - For men with PSA 1–3 ng/ml, repeat PSA testing every two years (Level of evidence: 3; Grade of recommendation: C).
 - For men with PSA >3 ng/ml, consider more frequent PSA testing intervals or adjunctive testing strategies (Level of evidence: 4; Grade of recommendation: C).
- For men electing to undergo PSA screening, we suggest that the age at which to discontinue PSA screening should be based on current PSA level and life expectancy
 - For men aged 60 with a PSA <1 ng/ml, consider discontinuing PSA screening (Level of evidence: 2; Grade of recommendation: C)
 - For all other men, discontinue PSA screening at age 70 (Level of evidence: 2; Grade of recommendation: C).
 - For men with a life expectancy less than 10 years, discontinue PSA screening (Level of evidence: 4; Grade of recommendation: C).
- The CUA does not recommend using PSAV alone for clinical decision-making in men undergoing routine screening; however, PSAV can provide additional information about a patient's risk of prostate cancer.

- Due to the lack of empirical validation, the use of PSAD alone for clinical decision-making is discouraged; however, use of PSAD can be considered adjunctively in men with known prostate volumes.
- The use of percent free PSA alone for clinical decision-making is not recommended; however, percent free PSA can be useful in estimating the risk of underlying disease in men with elevations in PSA (Level of evidence: 2; Grade of recommendation: C).

Canadian Agency for Drugs and Technologies in Health (CADTH): In the 2013 CADTH Prostate Cancer Screening: A Review of the Guidelines the authors aimed to evaluate the North American guidelines about the prostate cancer screening. A total of ten guidelines were retrieved. The report conclusions state that “With respect to the recommendations of the included guidelines, none of the included guidelines provided recommendations against prostate cancer screening for the general population. Most of the guidelines provided age criteria that limit screening for men between the ages of 40 or 50 up to the age of 70 or 75. Six guidelines recommended favorably on PSA-based screening for different age groups; on the other hand, one guideline by the USPSTF recommended against PSA testing for prostate cancer screening. This disagreement was mainly due to differences in the primary source of evidence included and the outcome priorities in each guideline.”

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD	National	Prostate Specific Antigen (190.31)	Nov 25, 2002
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

- Note:** 1) This list of codes may not be all-inclusive.
 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
84152	Prostate specific antigen (PSA); complexed (direct measurement)
84153	Prostate specific antigen (PSA); total
84154	Prostate specific antigen (PSA); free

HCPCS Codes	Description
G0103	Prostate cancer screening; prostate specific antigen test (PSA)

*Current Procedural Terminology (CPT®) ©2020 American Medical Association: Chicago, IL.

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