Cigna Medical Coverage Policy

Subject **Prostate-Specific Antigen (PSA) Screening for Prostate Cancer**

Effective Date 11/15/2013
Next Review Date 11/15/2014
Coverage Policy Number 0215

Table of Contents

Hyperlink to Related Coverage Policies

Gene-Based Testing for Prostate Cancer Screening, Detection and Disease Monitoring
High Intensity Focused Ultrasound (HIFU) for Prostate Cancer
Tumor Markers for Cancer and Serum Marker Panels for Liver Disease

INSTRUCTIONS FOR USE

*The following Coverage Policy applies to health benefit plans administered by Cigna companies. Coverage Policies are intended to provide guidance in interpreting certain **standard** Cigna benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supersedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of Cigna. Copyright ©2013 Cigna*

Coverage Policy

Cigna covers annual prostate-specific antigen (PSA) testing for prostate cancer screening 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 who are age 50 and over with a life expectancy of at least 10 years

Cigna covers percent free PSA (%fPSA), free-to-total PSA ratio (fPSA/tPSA) testing and/or complexed PSA (cPSA) testing as 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.

Cigna does not cover %fPSA (or fPSA/tPSA) testing or cPSA testing as screening tests for asymptomatic men in the general population because such testing is considered experimental, investigational or unproven.

General Background

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, it is more commonly used as an adjunct to DRE (Loeb, et al., 2011b; National Cancer Institute [NCI], 2013; U.S. Preventive Services Task Force [USPSTF], 2012.).

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, 2009). 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., 2011b).

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. Application of PSA derivatives age-adjusted values, and, more recently, molecular derivatives have been proposed to improve the performance of PSA (Getzenberg, et al., 2011; Barry, 2009).

Normal PSA levels are not well-defined. A PSA level that is considered low ranges from 0–2.5 ng/mL. A PSA level of 6–10 ng/mL is considered slightly to moderately elevated; levels between 10 and 19.9 ng/mL are considered moderately elevated. Anything above 20 ng/mL is considered significantly elevated. The higher the PSA, the more likely cancer may be present. Researchers have recognized that high-risk groups such as men with family histories of prostate cancer and African Americans may benefit from screening at an earlier age. It is recommended that baseline values be considered at age 40 (NCCN, 2012; NCI, 2013; Loeb, et al., 2006; Barry, 2001).

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 (NCCN, 2012; Loeb, et al. 2007). 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, 2012; Barry, 2009).

- **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, 2012; 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, 2012).

U.S. Food and Drug Administration (FDA)
A number of different manufacturers make PSA test kits (FDA, 2007). 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 published recently illustrate this controversy—Andriole et al. (2009; 2012) reported on results of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and Schröder et al. (2009; 2012) 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).

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.

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<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 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) Trial: 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 (NCI, 2012; 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.

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.

Djulbegovic 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 Randomised 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.

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.

In a prospective, nested case-control study, Gann et al. (2002) reported that %fPSA was significantly better than tPSA in discriminating cases with prostate cancer from controls without cancer only in the tPSA range of 4–10 ng/mL. Another large prospective study reported that, at a cutoff of 18–20%, %fPSA was effective in the tPSA range of 2–4 ng/mL, detecting approximately 50% of cancers while sparing up to 73% of unnecessary biopsies (Haese, et al., 2002). In contrast, results of a large retrospective study suggested that, in the narrow tPSA range of 2.6–4.0 ng/mL, %fPSA measurements provide risk assessment information about the presence of prostate cancer that are less robust than in the broader tPSA range of 4–10 ng/mL (Roehl, et al., 2002).

A large number of studies evaluated cPSA and/or cPSA-associated parameters, such as the ratio of cPSA to tPSA, or cPSA/tPSA. A specific assay for cPSA has been developed. Prior to its development, cPSA was derived by subtracting fPSA from tPSA (Brawer, et al., 2002). Brawer et al. (2000), in a retrospective multicenter study, reported that cPSA as a single test enhances the specificity for detecting prostate cancer and may serve as a single assay replacement. However, the patient populations identified by cPSA and %fPSA are different. Consistent with these results are those of three prospective studies. Miller et al. (2001), Hugosson et al. (2003) and Djavan et al. (2002) reported that cPSA and fPSA/tPSA performed equally well in differentiating between benign disease and prostate cancer, providing clinical benefits over the use of tPSA alone. The Saika et al. (2002) study results also concurred but used a different assay. One small prospective study reported that the overall diagnostic performance of cPSA was better than that of tPSA or fPSA/tPSA (Mitchell, et al., 2001). Another small prospective study reported that the use of cPSA alone improved prostate cancer detection over that of testing with tPSA and PSA ratios in individuals with tPSA values of 2–4 ng/mL (Horninger, et al., 2002). Babian et al. (2006) reported that a 2.2 ng/mL cPSA cutoff point decreases the number of unnecessary biopsies in the tPSA range of 2.5–6.0 ng/mL. The authors stated this suggests the potential value of cPSA as a first-line diagnostic test for early detection of prostate cancer.

A few studies have assessed the utility of PSAD for cancer detection. While both PSAD and %fPSA provided comparable results, %fPSA has the advantage in that its determination does not require the expense or inconvenience of TRUS. A prospective multicenter study reported that cPSA volume-related parameters, such as PSAD and cPSA of the transition zone, further improved the specificity of PSA in the early detection of prostate cancer in men with tPSA of 4–10 ng/mL (Djavan, et al., 2002).

In a systematic review and meta-analysis, Roddam et al. (2005) evaluated the diagnostic performance of fPSA to tPSA (f/tPSA) or cPSA for the detection of prostate cancer in men with PSA levels between 2–10 ng/mL. The authors took data on sensitivity and specificity from 66 eligible studies. The findings revealed the use of the f/tPSA or the cPSA improved diagnostic performance among men with a tPSA of 2–4 or 4–10 ng/mL compared to tPSA alone. The diagnostic performance of the f/tPSA test was significantly higher in the tPSA range of 4–10 ng/mL compared to a tPSA range of 2–4ng/mL. At a sensitivity of 95%, the specificity was 18% in the 4–10 ng/mL tPSA range and 6% in the 2–4 ng/mL tPSA range. The diagnostic performance of the f/tPSA test and the cPSA test was equivalent in both PSA ranges among studies that measured both isoforms. The authors

reported that, “The use of the f/tPSA or cPSA test among men with PSA levels between 2–10 ng/mL can reduce the number of unnecessary biopsies while maintaining a high cancer detection rate.”

Lee et al. (2006) conducted a meta-analysis of the diagnostic performance of the %fPSA test in determining prostate cancer status and to assess its value in helping to decide whether to biopsy the prostate. Forty-one studies were included in the meta-analysis containing 19,643 subjects. The authors reported that %fPSA can add modest clinical value to prostate cancer screening. In the “gray zone” of PSA testing (i.e., 4–10 ng/mL) %fPSA does improve information when values reach certain thresholds, suggesting that the false-positive rate of PSA testing will decrease only when %fPSA appears at these extreme values. The authors stated that fPSA seems to contribute more effectively as an adjunct test to primary prostate cancer screening under certain defined situations.

Professional Societies/Organizations

National Comprehensive Cancer Network (NCCN): The NCCN evidence-based Prostate Cancer Early Detection Guideline was developed for men who have specifically opted to participate in an early detection program (after receiving the appropriate counseling on the pros and cons of early detection). The authors state that their guidelines are not designed to address the controversy over whether to screen for prostate cancer. The NCCN guideline has suggested “talking points” for discussion with a potential screenee about the pros and cons of PSA testing “summarizing that there are advantages and disadvantages to having a PSA test, and there is no “right” answer about PSA testing for everyone. Each man should make an informed decision about whether the PSA test is right for him”. Additionally, the NCCN developed algorithms for prostate cancer detection. All the recommendations are category 2A (unless otherwise noted), which means there is uniform NCCN consensus, based on lower level evidence, including clinical experience, that the recommendation is appropriate. The NCCN guidelines recommend for men who choose PSA screening, baseline PSA screening with DRE should begin at age 40 (category 2B-the recommendation is based on lower-level evidence and there is nonuniform NCCN consensus[but no major disagreement]). The median PSA level is approximately 0.7 ng/mL for age 40-49. If the PSA is < 1.0 ng/mL, repeat the PSA at age 45. If at age 45 the PSA is ≤ 1.0 ng/mL, offer regular screening at age 50. If at age 45 the PSA is > 0.1 ng/mL, annual follow-up of DRE and PSA is recommended (category 2B). If, at age 40, the PSA is ≥ 1.0 ng/mL, or African-American, or family history or men taking 5 alpha –reductase inhibitors, do annual follow-up of DRE and PSA (category 2B). Men receiving 5-alpha reductase inhibitors (i.e., finasteride and dutasteride) have been associated with increased ability of PSA to detect high-grade prostate cancer. The 5-alpha reducatase inhibitors are commonly used to treat benign prostatic hyperplasia (BPH). This class of drugs generally results in an approximate 50% decrease in serum PSA levels after 6-12 months but the effect is tremendously variable. The NCCN guidelines recommend the use %fPSA as an alternative in the management of patients with normal DREs and tPSA levels between 4 and 10 ng/mL if there is a contraindication to biopsy. Use of cPSA has been approved as an aid in the detection of prostate cancer in men aged 50 years or older in conjunction with DRE. The guidelines state that cPSA has not gained widespread acceptance standard practice so it was not incorporated in their algorithms (NCCN, 2012). There has been no update to this guideline since 2012.

U.S. Preventive Services Task Force (USPSTF): The USPSTF recommends against prostate-specific antigen (PSA)-based screening for prostate cancer. The USPSTF assigned a Grade D recommendation to this statement since there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. This recommendation replaces the 2008 recommendation. Whereas the USPSTF previously recommended against PSA-based screening for prostate cancer in men aged 75 years and older and concluded that the evidence was insufficient to make a recommendation in younger men, the USPSTF now recommends against PSA-based screening for prostate cancer in all age groups (USPSTF, 2012).

In an evidence update for the USPSTF Lin et al. (2011) concluded that “Five randomized controlled trials (two fair- and three poor-quality) and two meta-analyses have evaluated the impact of PSA-based screening on prostate cancer mortality. After about 10 years, PSA-based screening is associated with the detection of additional cases of prostate cancer, but small to no reduction in prostate cancer-specific mortality.”

American Academy of Family Physicians (AAFP): The AAFP recommends against prostate-specific antigen (PSA)-based screening for prostate cancer (AAFP, 2012).

American College of Physicians (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".

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 before age 65 years) should receive this information beginning at age 40 years (Wolf, et al., 2010).

National Cancer Institute (NCI): The NCI summary of evidence for prostate cancer screening addressing benefits stating, "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 show no effect on mortality through 7 years but are inconsistent beyond 7 to 10 years". The summary of evidence for harms states that "based on solid evidence, screening with PSA and/or DRE detects 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. Whatever the screening modality, 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, 2013).

American Urological Association (AUA): In 2013, the AUA published a new Clinical Guideline on the Early Detection of Prostate Cancer. 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."

The National Academy of Clinical Biochemistry (NACB): The NACB recommendations for the clinical use of PSA serum markers in the management of prostate cancer states that "A decision as to whether widespread implementation of PSA screening for prostate cancer in the general population can be recommended must await the outcome of ongoing prospective randomized screening studies (e.g., ERSPC trial in Europe) which are due to be completed by 2010". This was assigned a level of evidence of III (i.e., large prospective studies) and an expert opinion strength of recommendation of A (i.e., high, further research is very unlikely to change the panel's confidence in the estimate). The NACB recommendation states that the use of %fPSA is "recommended as an aid in distinguishing men with prostate cancer from men with benign prostatic hypertrophy when the total PSA level in serum is within the range of 4–10 ng/mL and DRE is negative, most frequently in men undergoing repeat biopsy, in selected high-risk groups and particularly in identifying men who have prostate cancer despite initial negative biopsy findings. The clinical decision limit must be properly validated for each combination of fpSA and total PSA assays". This was assigned a level of evidence of I (i.e., evidence from a single, high-powered, prospective, controlled study that is specifically designed to test marker, or evidence from a meta-analysis, pooled analysis or overview of level II or III studies) and an expert opinion strength of recommendation of A (Sturgeon, et al., 2008). There has been no update to this recommendation since 2008.

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.

Use Outside of the US

European Society for Medical Oncology (ESMO): The ESMO Prostate Cancer Clinical Practice Guidelines for diagnosis, treatment and follow-up states that, "Decisions on population screening await longer follow-up and the results of analyses of cost-effectiveness and quality of life [I, B]. Serum PSA should be measured and digital rectal examination (DRE) performed in appropriately counseled patients in whom there is clinical suspicion of prostate cancer or in those who wish to be screened. The decision whether or not to have a prostate biopsy should be made in the light of PSA parameters such as free PSA, PSA velocity and PSA density, DRE findings,

prostate size, ethnicity, age, comorbidities, patient values and history of previous biopsy [II, B]." Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty (Horwich, et al., 2010).

European Association of Urology (EAU): The EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Treatment of Clinically Localized Disease states, "There is currently no evidence for introducing widespread population-based screening programmes for early prostate cancer detection in all men (LE: 2)." "The decision to undergo early PSA testing should be a shared decision between the patient and his physician based on information balancing its advantages and disadvantages. A baseline PSA determination at 40 yr of age has been suggested on which the subsequent screening interval may then be based (GR: B)." To facilitate evaluating the quality of the information provided, level of evidence (LE) and grade of recommendation (GR) have been inserted according to the general principles of evidence-based medicine (Heidenreich, et al., 2011).

Canadian Urological Association (CUA): The 2011 Prostate Cancer Screening Guidelines state that these Guidelines are recommendations; they are not a standard of care for all patients and should not pre-empt a physician's clinical judgment. For prostate cancer screening tests the authors state that "Digital rectal examination and PSA are the first line prostate cancer screening tests)". The authors state that, "Contemporary prostate cancer screening for men with at least a 10-year life expectancy now involves more than just a DRE and PSA. No single PSA value should be the only determinant of whether or not to biopsy a patient. The prostate-specific antigen velocity (PSAV), PSAD and PSA free to total ratio may improve PSA sensitivity and specificity. Furthermore, nomograms and mathematical models may guide a clinician by combining multiple clinical variables, such as DRE, PSA, PSAV, PSA isoforms, age, race, family history of prostate cancer and genetic data to determine the risk of prostate cancer and the risk of biologically significant disease. Some guidelines recommend prostate cancer screening at age 40, particularly for those at higher risk" (Izawa, et al., 2011).

Summary
At this time, evidence that prostate-specific antigen (PSA) testing for prostate cancer screening reduces long-term mortality is lacking. It is recommended that health care professionals discuss the possible benefits, side effects, and questions about prostate-specific antigen (PSA) testing for prostate cancer screening so that men can make informed decisions taking into account their own situation and risk. There is sufficiently promising evidence from large-scale observational studies to conclude that PSA in conjunction with DRE can detect potentially curable prostate cancer. In addition, 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. Ongoing randomized clinical trials are being conducted to address the benefits of PSA-based prostate cancer screening.

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.

Covered when medically necessary:

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)

References

1. American Academy of Family Physicians (AAFP). Clinical Recommendations. Prostate Cancer. 2012. Accessed October 6, 2013. Available at URL address: http://www.aafp.org/online/en/home/clinical/exam/prostatecancer.html

2. American Cancer Society (ACS). Detailed cancer guide. Can prostate cancer be found early? Last revised Sept 4, 2012. Accessed October 6, 2013. Available at URL address: http://www.cancer.org/cancer/index

3. American Urological Association (AUA). Prostate-specific antigen (PSA) best practice statement. 2009. Accessed October 6, 2013. Available at URL address: http://www.auanet.org/guidelines/

4. Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al; PLCO Project Team. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst. 2012 Jan 18;104(2):125-32. Epub 2012 Jan 6.

5. Andriole GL, Grubb RL 3rd, Buys SS, Chia D, Church TR, Fouad MN, et al.; PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009 Mar 26;360 (13):1310-9. Epub 2009 Mar 18.

6. Andriole GL, Levin DL, Crawford ED, Gelmann EP, Pinsky PF, Chia D, et al; PLCO Project Team. Prostate Cancer Screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: findings from the initial screening round of a randomized trial. J Natl Cancer Inst. 2005 Mar 16;97(6):433-8.

7. Aus G, Bergdahl S, Lodding P, Lilja H, Hugosson J. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer--results from a prospective, population-based randomized controlled trial. Eur Urol. 2007 Mar;51(3):659-64.

8. Auvinen A, Maattanen L, Finne P, Stenman UH, Aro J, Juusela H, et al. Test sensitivity of prostate-specific antigen in the Finnish randomised prostate cancer screening trial. Int J Cancer. 2004 Oct 10;111(6):940-3.

9. Bangma CH, Rietbergen JB, Kranse R, Blijenberg BG, Petterson K, Schröder FH. The free-to-total prostate specific antigen ratio improves the specificity of prostate specific antigen in screening for prostate cancer in the general population. J. Urol. 1997;157(6):2191-6.

10. Barry MJ. Screening for prostate cancer. In: Goroll AH, Mulley AG, editors. Primary Care Medicine: Office Evaluation and Management of the Adult Patient. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009. Ch. 126.

11. Boniol M, Boyle P, Autier P, Ruffion A, Perrin P. Critical role of prostate biopsy mortality in the number of years of life gained and lost within a prostate cancer screening programme. BJU Int. 2012 Dec;110(11):1648-52.

12. Brawer MK, Cheli CD, Neaman IE, Goldblatt J, Smith C, Schwartz MK, et al. Complexed prostate specific antigen provides significant enhancement of specificity compared with total prostate specific antigen for detecting prostate cancer. J Urol. 2000;163(5):1476-80.

13. Brawer MK. Clinical usefulness of assays for complexed prostate-specific antigen. Urol Clin North Am. 2002;29(1):193-203.

14. Carter HB, Ferrucci L, Kettermann A, Landis P, Wright EJ, Epstein JI, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. J Natl Cancer Inst. 2006 Nov 1;98(21):1521-7.

15. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al. Early detection of prostate cancer: AUA Guideline. J Urol. 2013 Aug;190(2):419-26.

16. Catalona WJ, Beiser JA, Smith DS. Serum free prostate specific antigen and prostate specific antigen density measurements for predicting cancer in men with prior negative prostatic biopsies. J Urol. 1997a;158(6):2162-7.

17. Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA. 1998;279(19):1542-7.

18. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination: enhancement of specificity with free PSA measurements. JAMA. 1997b;277(18):1452-5.

19. Catalona WJ, Southwick PC, Slawin KM, Partin AW, Brawer MK, Flanigan RC, et al. Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. Urology. 2000;56(2):255-60.

20. Cheli CD, Levine RL, Cambetas DR, Kolker JD, Roberts SB. Age-related reference ranges for complexed prostate-specific antigen and complexed/total prostate-specific antigen ratio: results from East Texas Medical Center Cancer Institute screening campaign. Urology. 2002;60(4 Suppl 1):53-9.

21. Chou R, Croswell JM, Dana T, Bougatsos C, Blazina I, Fu R, et al. Screening for Prostate Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2011 Oct 7.

22. Chou R, Croswell JM, Dana T, Bougatsos C, Blazina I, Fu R, et al. Screening for Prostate Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force. AHRQ Publication No. 12-05160-EF-3. October 2011. Accessed October 6, 2013. Available at URL address: http://www.uspreventiveservicestaskforce.org/uspstf12/prostate/prostateart.htm

23. Crawford ED, Grubb R 3rd, Black A, Andriole GL Jr, Chen MH, Izmirlian G, et al. Comorbidity and mortality results from a randomized prostate cancer screening trial. J Clin Oncol. 2011 Feb 1;29(4):355-61. Epub 2010 Nov 1.

24. Crawford ED, Leewansangtong S, Goktas S, Holthaus K, Baier M. Efficiency of prostate-specific antigen and digital rectal examination in screening, using 4.0 ng/ml and age-specific reference range as a cutoff for abnormal values. Prostate. 1999;38(4):296-302.

25. Crawford ED, Pinsky PF, Chia D, Kramer BS, Fagerstrom RM, Andriole G, et al. Prostate specific antigen changes as related to the initial prostate specific antigen: data from the prostate, lung, colorectal and ovarian cancer screening trial. J Urol. 2006 Apr;175(4):1286-90; discussion 1290.

26. Djavan B, Remzi M, Zlotta AR, Ravery V, Hammerer P, Reissigl A, et al. Complexed prostate-specific antigen, complexed prostate-specific antigen density of total and transition zone, complexed/total prostate-specific antigen ratio, free-to-total prostate-specific antigen ratio, density of total and transition zone prostate-specific antigen: results of the prospective multicenter European trial. Urology. 2002;60(4 Suppl 1):4-9.

27. Djulbegovic M, Beyth RJ, Neuberger MM, Stoffs TL, Vieweg J, et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. BMJ. 2010 Sep 14;341:c4543. doi: 10.1136/bmj.c4543.

28. Filella X, Alcover J, Molina R, Corral JM, Carretero P, Ballesta AM. Measurement of complexed PSA in the differential diagnosis between prostate cancer and benign prostate hyperplasia. Prostate. 2000;42(3):181-5.

29. Gann PH, Ma J, Catalona WJ, Stampfer MJ. Strategies combining total and percent free prostate specific antigen for detecting prostate cancer: a prospective evaluation. J Urol. 2002;167(6):2427-34.

30. Getzenberg RH, Partin AW. Prostate Cancer Tumor Markers. In: Wein, AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Wein: Campbell-Walsh Urology. 10th ed. Philadelphia, PA: Saunders Elsevier; 2011. Ch 98.

31. Greene KL, Albertsen PC, Babaian RJ, Carter HB, Gann PH, Han M, et al. Prostate specific antigen best practice statement: 2009 update. J Urol. 2009 Nov;182(5):2232-41.

32. Haese A, Dworschack RT, Partin AW. Percent free prostate specific antigen in the total prostate specific antigen 2 to 4 ng./ml. range does not substantially increase the number of biopsies needed to detect clinically significant prostate cancer compared to the 4 to 10 ng./ml. range. J Urol. 2002;168(2):504-8.

33. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al; European Association of Urology. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol. 2011 Jan;59(1):61-71.

34. Horninger W, Cheli CD, Babaian RJ, Fritsche HA, Lepor H, Taneja SS, et al. Complexed prostate-specific antigen for early detection of prostate cancer in men with serum prostate-specific antigen levels of 2 to 4 nanograms per milliliter. Urology. 2002;60(4 suppl 1):31-5.

35. Horwich A, Parker C, Bangma C, Kataja V; ESMO Guidelines Working Group. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010 May;21 Suppl 5:v129-33.

36. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. 2010 Aug;11(8):725-32. Epub 2010 Jul 2.

37. Ilic D, O'Connor D, Green S, Wilt T. Screening for prostate cancer. Cochrane Database Syst Rev. 2006 Jul 19;3:CD004720.

38. Ilic D, O'Connor D, Green S, Wilt TJ. Screening for prostate cancer: an updated Cochrane systematic review. BJU Int. 2011 Mar;107(6):882-91. doi: 10.1111/j.1464-410X.2010.10032.x.

39. Izawa JI, Klotz L, Siemens DR, Kassouf W, So A, Jordan J, et al. Prostate cancer screening: Canadian guidelines 2011. Can Urol Assoc J. 2011 Aug;5(4):235-40. doi: 10.5489/cuaj.11134.

40. Kilpeläinen TP, Tammela TL, Malila N, Hakama M, Santti H, Määttänen L, et al. Prostate cancer mortality in the Finnish randomized screening trial. J Natl Cancer Inst. 2013 May 15;105(10):719-25.

41. Kjellman A, Akre O, Norming U, Törnblom M, Gustafsson O. 15-year followup of a population based prostate cancer screening study. J Urol. 2009 Apr;181(4):1615-21; discussion 1621. Epub 2009 Feb 23.

42. Kwiatkowski M, Huber A, Moschopulos M, Lehmann K, Wernli M, Hafeli A, Recker F. Prostate cancer screening: results of a prospective trial in Canton Aargau, Switzerland. Swiss Med Wkly. 2004 Oct 2;134(39-40):580-5.

43. Labrie F, Candas B, Cusan L, Gomez JL, Belanger A, Brousseau G, et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. Prostate. 2004;59(3):311-8.

44. Labrie F, Candas B, Dupont A, Cusan L, Gomez JL, Suburu RE, et al. Screening decreases prostate cancer death: first analysis of the 1988 Quebec prospective randomized controlled trial. Prostate. 1999;38(2):83-91.

45. Lane JA, Howson J, Donovan JL, Goepel JR, Dedman DJ, Down L, et al. Detection of prostate cancer in unselected young men: prospective cohort nested within a randomised controlled trial. BMJ. 2007 Dec 1;335(7630):1139.

46. Lee R, Localio AR, Armstrong K, Malkowicz SB, Schwartz JS; Free PSA Study Group. A meta-analysis of the performance characteristics of the free prostate-specific antigen test. Urology. 2006 Apr;67(4):762-8.

47. Lilja H, Cronin AM, Dahlin A, Manjer J, Nilsson PM, Eastham JA, Bjartell A, Set al. Prediction of significant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50. Cancer. 2011 Mar 15;117(6):1210-9. doi: 10.1002/cncr.25568. Epub 2010 Oct 19.

48. Lin K, Croswell JM, Koenig H, et al. Prostate-Specific Antigen-Based Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 Oct. (Evidence Syntheses, No. 90.). Accessed October 6, 2013 Available at URL address: http://www.ncbi.nlm.nih.gov/books/NBK82303/

49. Lim LS, Sherin K; ACPM Prevention Practice Committee. Screening for prostate cancer in U.S. men ACPM position statement on preventive practice. Am J Prev Med. 2008 Feb;34(2):164-70.

50. Loeb S, Carter HB. Diagnosis and staging of prostate cancer. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Wein: Campbell-Walsh Urology. 10th ed. Philadelphia, PA: Saunders Elsevier; 2011b. Ch 99.

51. Loeb S, Catalona WJ. Prostate-specific antigen in clinical practice. Cancer Lett. 2007 Apr 28;249(1):30-9.

52. Loeb S, Catalona WJ. Prostate-specific antigen in clinical practice. Long-term radical prostatectomy outcomes among participants from the European Randomized Study of Screening for Prostate Cancer (ERSPC) Rotterdam. BJU Int. 2012 Dec;110(11):1678-83.

53. Loeb S, Roehl KA, Antenor JA, Catalona WJ, Suarez BK, Nadler RB. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. Urology. 2006 Feb;67(2):316-20.

54. Määttänen L, Auvinen A, Stenman UH, Rannikko S, Tammela T, Aro J, et al. European randomized study of prostate cancer screening: first-year results of the Finnish trial. Br J Cancer. 1999;79(7-8):1210-4.

55. Miller MC, O'Dowd GJ, Partin AW, Veltri RW. Contemporary use of complexed PSA and calculated percent free PSA for early detection of prostate cancer: impact of changing disease demographics. Urology. 2001;57(6):1105-11.

56. Mitchell ID, Croal BL, Dickie A, Cohen NP, Ross I. A prospective study to evaluate the role of complexed prostate specific antigen and free/total prostate specific antigen ratio for the diagnosis of prostate cancer. J Urol. 2001;165(5):1549-53.

57. Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012 Jul 17;157(2):120-34.

58. National Cancer Institute (NCI). Prostate Cancer Screening (PDQ®). Health Professional. Bethesda (MD): National Cancer Institute. Last modified Sept 27, 2013. Accessed October 6, 2013. Available at URL address: http://cancer.gov/

59. National Cancer Institute (NCI) Cancer Information Service (CIS). Prostate-Specific Antigen (PSA) Test. Reviewed July 24, 2012. Accessed October 6, 2013. Available at URL address: http://www.cancer.gov/cancertopics/factsheet/Detection/PSA

60. National Comprehensive Cancer Network (NCCN). Prostate cancer early detection. Volume 2.2012. Accessed October 6, 2013. Available at URL address: http://www.nccn.org/

61. National Institute for Clinical Excellence (NICE). Prostate cancer: diagnosis and treatment. Full guidance: CG58. London, UK: NICE; February 2008. Accessed October 6, 2013. Available at URL address: http://www.nice.org.uk/

62. Nelson WG, Carter HB, DeWeese TL, Eisenberger MA. Prostate cancer. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. Abeloff: Clinical Oncology. 4th ed. Philadelphia, PA: Churchill Livingstone; 2008. Ch. 88.

63. Okihara K, Cheli CD, Partin AW, Fritche HA, Chan DW, Sokoll LJ, et al. Comparative analysis of complexed prostate specific antigen, free prostate specific antigen and their ratio in detecting prostate cancer. J Urol. 2002;167(5):2017-24.

64. Okihara K, Ukimura O, Nakamura T, Ushijima S, Mizutani Y, Kawauchi A, et al. Complexed PSA improves prostate cancer detection: results from a multicenter Japanese clinical trial. Urology. 2006 Feb;67(2):328-32.

65. Pinsky PF, Black A, Parnes HL, Grubb R, David Crawford E, Miller A, et al. Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer Epidemiol. 2012 Dec;36(6):e401-6. Cancer Epidemiol. 2012 Dec;36(6):e401-6.

66. Qaseem A, Barry MJ, Denberg TD, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Screening for prostate cancer: a guidance statement from the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2013 May 21;158(10):761-9.

67. Roddam AW, Duffy MJ, Hamdy FC, Ward AM, Patnick J, Price CP, et al; On behalf of the NHS Prostate Cancer Risk Management Programme. Use of prostate-specific antigen (PSA) isoforms for the detection of prostate cancer in men with a PSA level of 2-10 ng/ml: systematic review and meta-analysis. Eur Urol. 2005 Sep;48(3):386-99; discussion 398-9.

68. Roehl KA, Antenor JA, Catalona WJ. Robustness of free prostate specific antigen measurements to reduce unnecessary biopsies in the 2.6 to 4.0 ng./ml. range. J Urol. 2002;168(3):922-5.

69. Roobol MJ, Grenabo A, Schröder FH, Hugosson J. Interval cancers in prostate cancer screening: comparing 2- and 4-year screening intervals in the European Randomized Study of Screening for Prostate Cancer, Gothenburg and Rotterdam. J Natl Cancer Inst. 2007 Sep 5;99(17):1296-303.

70. Roobol MJ, Schröder FH, Kranse R; ERSPC, Rotterdam. A comparison of first and repeat (four years later) prostate cancer screening in a randomized cohort of a symptomatic men aged 55-75 years using a biopsy indication of 3.0 ng/ml (results of ERSPC, Rotterdam). Prostate. 2006 May 1;66(6):604-12.

71. Saika T, Tsushima T, Nasu Y, Kusaka N, Miyaji Y, Takamoto H, et al. Prostate specific antigen complexed to α-1-antichymotrypsin in patients with intermediate prostate specific antigen levels. Cancer. 2002;94(6):1685-91.

72. Sandblom G, Varenhorst E, Rosell J, Löfman O, Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. BMJ 2011;342:d1539. doi:10.1136/bmj.d1539.

73. Schröder FH, Hugosson J, Carlsson S, Tammela T, Määttänen L, Auvinen A, et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol. 2012b Nov;62(5):745-52.

74. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al; ERSPC Investigators. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med. 2012a Mar 15;366(11):981-90.

75. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al.; ERSPC Investigators. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009 Mar 26;360(13):1320-8. Epub 2009 Mar 18.

76. Shao YH, Albertsen PC, Roberts CB, Lin Y, Mehta AR, Stein MN, et al. Risk profiles and treatment patterns among men diagnosed as having prostate cancer and a prostate-specific antigen level below 4.0 ng/ml. Arch Intern Med. 2010 Jul 26;170(14):1256-61.

77. Smith RA, Cokkinides V, Eyre HJ; American Cancer Society. American Cancer Society guidelines for the early detection of cancer, 2003. CA Cancer J Clin. 2003 Jan-Feb;53(1):27-43.

78. Sturgeon CM, Duffy MJ, Stenman UH, Lilja H, Brünner N, Chan DW, et al.; National Academy of Clinical Biochemistry. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. Clin Chem. 2008 Dec;54(12):e11-79.

79. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health (CDRH). Product code LTJ. Updated Sept 30, 2013. Accessed October 6, 2013. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

80. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health (CDRH). AxSYM Free PSA. P980007. Accessed October 6, 2013. Approved February 5, 2004. Updated June 4, 2004. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=p980007

81. U.S. Preventive Services Task Force (USPSTF). Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008 Aug 5;149(3):185-91.

82. U.S. Preventive Services Task Force (USPSTF). Screening for Prostate Cancer: May 2012. Accessed October 6, 2013. Available at URL address: http://www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm

83. Vashi AR, Wojno KJ, Henricks W, England BA, Vessella RL, Lange PH, et al. Determination of the “reflex range” and appropriate cutpoints for percent free prostate-specific antigen in 413 men referred for prostatic evaluation using the AxSYM system. Urology. 1997;49(1):19-27.

84. Vessella RL, Lange PH, Partin AW, Chan DW, Sokoll LJ, Sasse EA, Crawford ED. Probability of prostate cancer detection based on results of a multicenter study using the AxSYM free PSA and total PSA assays. Urology. 2000;55(6):909-14.

85. Wallner LP, Jacobsen SJ. Prostate-specific antigen and prostate cancer mortality: a systematic review. Am J Prev Med. 2013 Sep;45(3):318-26

86. Wilkinson J, Bass C, Diem S, Gravley A, Harvey L, Maciosek M, et al. Institute for Clinical Systems Improvement. Preventive Services for Adults. Updated September 2013.

87. Wolf AM, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ, et al; American Cancer Society Prostate Cancer Advisory Committee. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin. 2010 Mar-Apr;60(2):70-98. Epub 2010 Mar 3.