



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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

**Effective Date** ..... 11/15/2010  
**Next Review Date** ..... 11/15/2011  
**Coverage Policy Number** ..... 0215

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## Hyperlink to Related Coverage Policies

Gene-Based Testing for Prostate Cancer Screening, Detection and Disease Monitoring

Prostate Saturation Biopsy

Transrectal Ultrasound

Tumor Markers for Diagnosis and Management of Cancer

### INSTRUCTIONS FOR USE

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## Coverage Policy

**CIGNA covers annual prostate-specific antigen (PSA) testing for prostate cancer screening for EITHER of the following:**

- for asymptomatic men at any age 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.**

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## 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. Due to its low specificity and positive predictive value (PPV), TRUS may have a more useful role in the diagnostic workup of an abnormal screening test, rather than as a primary screening test. For example, TRUS guidance is the most frequent method of directing prostate needle biopsy in patients with an abnormal DRE or PSA (National Cancer Institute [NCI], 2010b; NCI, 2009a; Agency for Healthcare Research and Quality [AHRQ], 2008; Carter, et al., 2007).

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).

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 (Barry, 2009; Gretzer, et al., 2007).

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. In a patient with mildly abnormal levels, it is recommended that the PSA test be repeated to ensure that the results are consistent. The PSA-based criteria used to recommend a diagnostic prostate biopsy have evolved over time. These evolving criteria aim to increase the sensitivity of the test for younger men more likely to die of the disease and to reduce the frequency of detecting cancers of low malignant potential in elderly men more likely to die of other causes. The PSA cutoff of 4 ng/mL for screening is arbitrary and is designed to reliably detect prostate cancer at an early stage. This low cutoff value, however, is associated with an appreciable number of false-positive findings, which diminishes the test's predictive value and results in unnecessary biopsies for those with benign conditions. Moreover, the use of this cutoff is associated with a false-negative rate of 20% (i.e., approximately 20% of men with diagnosed prostate cancer have PSA levels below 4 ng/mL). Recent research has found prostate cancer in men with PSA levels below 4.0 ng/mL. Lowering the threshold to 2.6 ng/mL could double the rate of detecting cancer in men under age 60 with little loss of specificity. Age-specific reference ranges apply a lower "upper" limit of normal for younger males

and a higher "upper" limit for older individuals. Different thresholds alter sensitivity and specificity of detection. The threshold for performance of a biopsy is now 2.6 ng/mL for men under age 60. Age 50 is traditionally the age for starting to consider PSA screening. 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. Those whose total PSA value is  $\geq$  the median level (i.e.,  $> 0.6$  ng/mL) may consider annual screening (NCCN, 2010; NCI, 2009; 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, 2010; 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 (NCI, 2010a; NCCN, 2010; 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  $\geq 0.35$  ng/mL is suspicious for the presence of cancer, and biopsy is recommended. For men with PSA 4–10 ng/mL, PSA velocity of  $\geq 0.75$  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, 2010; 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). Values  $< 0.10$  are consistent with BPH, while those  $> 0.15$  suggest cancer. The lack of precision of measurement of both PSA and prostate volume has prevented the widespread clinical use of PSAD (NCCN, 2010).

### 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) reported on results of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and Schröder et al. (2009) 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.

**Clinical Studies Evaluating PSA Screening for Prostate Cancer:** The European Randomized Study of Screening for Prostate Cancer (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).

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:**

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. (2006) conducted a 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. Two RCTs with a total of 55,512 participants were included; however, both trials had methodological weaknesses. A meta-analysis of the data extracted from these studies indicated no statistically significant difference in prostate cancer mortality between men randomized for prostate cancer screening and those randomized to control. Neither study assessed the effect of prostate cancer screening on quality of life, all-cause mortality or cost effectiveness. The authors reported that, “Given that only two RCTs were included, and the high risk of bias of both trials, there is insufficient evidence to either support or refute the routine use of mass, selective or opportunistic screening compared to no screening for reducing prostate cancer mortality. Currently, no robust evidence from RCTs is available regarding the impact of screening on quality of life, harms of screening, or its economic value. Results from two ongoing large-scale multicenter RCTs that will be available in the next several years are required to make evidence-based decisions regarding prostate cancer screening” (Ilic, et al., 2006).

**Ongoing Trials:** The NCI is sponsoring a large RCT, the Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (PLCO), to determine whether screening with PSA and DRE will reduce prostate cancer mortality (NCI, 2008b). 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. The final results of the PLCO trial are still several years away.

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, 2009a, Andriole, et al., 2009).

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.”

**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. (2006) 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 2–4 ng/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**

No major scientific or medical organizations, including the American Cancer Society (ACS), American Urological Association (AUA), US Preventive Services Task Force (USPSTF), American College of Physicians (ACP), National Cancer Institute (NCI), American Academy of Family Physicians (AAFP), and American College of Preventive Medicine (ACPM) support routine testing for prostate cancer at this time. These organizations (the ACS, AUA, ACP, NCI, AAFP, ACPM, and the USPSTF) recommend that health care professionals discuss the possible benefits, side effects, and questions about early prostate cancer detection and treatment so that men can make informed decisions taking into account their own situation and risk (ACS, 2009).

**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. Additionally, the NCCN developed algorithms for prostate cancer detection. All the recommendations are category 2A, 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. 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 > 0.6 ng/mL, annual follow-up of DRE and PSA is recommended. If, at age 40, the PSA is ≥ 1.0 ng/mL, or African-American, or family history, do annual follow-up of DRE and PSA. The NCCN

guidelines recommend the use %fPSA or cPSA 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. The guidelines state that cPSA has not gained widespread acceptance standard practice so it was not incorporated in their algorithms (NCCN, 2010).

**American Cancer Society (ACS):** In 2009 the ACS published a guideline for the early detection of prostate cancer. The ACS 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. (Wilson et al., 2010).

**National Cancer Institute (NCI):** The NCI summary of evidence for prostate cancer screening 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” (NCI, 2010a).

**American Urological Association (AUA):** In 2009, the AUA updated their prostate specific antigen best practice statement. The AUA states there are two notable differences in this update, “First, the age for obtaining a baseline PSA has been lowered to 40 years. Secondly, the current policy no longer recommends a single, threshold value of PSA which should prompt prostate biopsy. Rather, the decision to proceed to prostate biopsy should be based primarily on PSA and Digital Rectal Examination (DRE) results, but should take into account multiple factors including free and total PSA, patient age, PSA velocity, PSA density, family history, ethnicity, prior biopsy history and comorbidities. In addition, although recently published trials show different results with regard to the impact of prostate cancer screening on mortality, both suggest that prostate cancer screening leads to overdetection and overtreatment of some patients. Therefore, the AUA strongly supports that men be informed of the risks and benefits of prostate cancer screening before biopsy and the option of active surveillance in lieu of immediate treatment for certain men newly diagnosed with prostate cancer” (AUA, 2009).-

**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).

**U.S. Preventive Services Task Force (USPSTF):** In 2008, the USPSTF updated their 2002 recommendations on screening for prostate cancer. The USPSTF evaluated randomized controlled trials of the benefits of prostate

cancer screening; cohort and cross-sectional studies of the psychological harms of false-positive PSA test results; and evidence on the natural history of prostate specific antigen–detected prostate cancer to address previously identified gaps in the evidence from the 2002 USPSTF recommendation. The USPSTF concludes that current evidence is insufficient to assess the balance of benefits and harms of screening for prostate cancer in men younger than age 75 years. The USPSTF graded this recommendation as a Grade I statement meaning that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. Additionally, the USPSTF recommends not screening for prostate cancer in men age 75 years or older. 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 (USPSTF, 2008).

Other highlights of the Task Force recommendations include: (1) given the uncertainties and controversy surrounding prostate cancer screening in men younger than age 75 years, clinicians who order the PSA test should not do so without first discussing with patients its potential but uncertain benefits and known harms of prostate cancer screening and treatment, should inform men of the gaps in the evidence, and should assist them in considering their personal preferences before deciding whether to be tested; (2) if early detection through screening does improve health outcomes, those most likely to benefit would be men age 50–74 years old. Even if prostate cancer screening is determined to be effective, the length of time required to experience a mortality benefit is greater than 10 years. Because a 75-year-old man has an average life expectancy of about 10 years, very few men age 75 years or older would experience a mortality benefit. Similarly, men younger than age 75 years who have chronic medical problems and a life expectancy of fewer than 10 years are also unlikely to benefit from screening and treatment; (3) PSA testing is more sensitive than DRE for the detection of prostate cancer; (4) the yield of screening in terms of cancer detected declines rapidly with repeated annual testing, and PSA screening as infrequent as very four years could yield as much benefit as annual screening; (5) older men, African-American men, and men with a family history of prostate cancer are at increased risk for diagnosis of and death from prostate cancer but the gaps in the evidence regarding potential benefits of screening applies to these men (USPSTF, 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).

### 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.

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## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

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

<b>HCPCS</b> <b>Codes</b>	<b>Description</b>
G0103	Prostate cancer screening; prostate specific antigen test (PSA), total

<b>ICD-9-CM</b> <b>Diagnosis</b> <b>Codes</b>	<b>Description</b>
790.93	Elevated prostate specific antigen (PSA)
V16.42	Family history of malignant neoplasm of prostate
V76.44	Special screening for malignant neoplasm of prostate
V84.03	Genetic susceptibility to malignant neoplasm of prostate

\*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	11/15/2007	0215	Prostate-Specific Antigen (PSA) Screening for Prostate Cancer

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.