PROSTATE SPECIFIC ANTIGEN
CARCINOMA OF THE PROSTATE

CLINICAL CORRELATION

DIAGNOSIS

▪ OFTEN “OCCULT”
  ▪ CLINICALLY INAPPARENT
  ▪ MICROSCOPIC LESIONS AT AUTOPSY OR RANDOM BIOPSY
  ▪ 30% OF ALL 50 Y/O MEN; UP TO 70% OF MEN > 80 Y/O

▪ DIGITAL RECTAL EXAM (DRE)
  ▪ MAY DETECT SOME EARLY CANCERS BECAUSE OF THEIR POSTERIOR LOCATION
  ▪ LOW SENSITIVITY + LOW SPECIFICITY

▪ PROSTATIC IMAGING STUDIES
  ▪ POOR SENSITIVITY + POOR SPECIFICITY

▪ TRANSRECTAL ULTRASOUND (TRUS)-GUIDED PROSTATE NEEDLE BIOPSY
  ▪ REQUIRED TO CONFIRM THE DIAGNOSIS !!!

▪ PELVIC LYMPHADENECTOMY
  ▪ STAGING PROCEDURE

▪ RADIONUCLIDE BONE SCAN
  ▪ OSSEOUS METASTASES → ↑ SERUM ALKALINE PHOSPHATASE
Prostate Cancer Screening Guidelines

- Risks and benefits of screening should be discussed with all at risk individuals
- All men age 50 and older
  - Annual PSA
  - Annual DRE
- Begin at age 45 for men in high risk groups
  - African Americans
  - Affected first degree relatives
Screening with a blood test for prostate specific specific antigen (PSA).
Prostate-specific antigen (PSA) is a glycoprotein protease secreted exclusively by the prostate epithelium, and substance released into a man's blood by his prostate gland. PSA is a glycoprotein protease secreted exclusively by the prostate epithelium.

A PSA test measures the amount of prostate-specific antigen in the blood.

Low amounts of PSA may be found in the blood of healthy men, but the amount of PSA in the blood normally increases as a man's prostate enlarges with age, as well as in prostate disease or trauma states.

Most men have levels under 4 nanograms per milliliter (ng/mL) of blood.
Prostate

Prostatic ducts

Prostate Specific Antigen

Absorption into the bloodstream

Free PSA

ACT bound PSA

αMG bound PSA
Indications for the PSA test.

- The prostate-specific antigen (PSA) test is done to:
  - Screen men for prostate cancer.
  - Monitor the development of prostate cancer and the response to treatment.
  - A PSA test is an effective screening test for prostate cancer. However, other medical conditions can cause high PSA levels; therefore, other tests (such as a prostate biopsy) are needed to confirm a diagnosis of prostate cancer.
How To Prepare

• Before having a test for prostate-specific antigen (PSA), patients should:
  • Refrain from sexual activity for 2 to 3 days prior to testing.
  • Wait several weeks after having a cystoscopy.
  • Wait until a urinary tract infection or prostatitis has cleared up.
• Normal values may vary from lab to lab.

• Because normal prostate-specific antigen (PSA) levels seem to increase with age, age-specific ranges may be used. However, the use of age-specific ranges is controversial and some health professionals prefer to use one range for all ages.
• Most men have levels under 4 nanograms per milliliter (ng/mL) of blood.
• PSA levels from 4 to 10 ng/mL are borderline.
• When prostate cancer develops, the PSA level usually goes above 4. Patients with levels in the borderline range between 4 and 10, have about a 25% chance of having prostate cancer.
• About 20% to 30% of men (20 to 30 men in 100) with PSA levels in this range have prostate cancer.
• A transrectal ultrasound (TRUS) and prostate biopsy are needed to confirm cancer.
• PSA levels above 10 ng/mL are high.
• If it is more than 10, the chance of having prostate cancer is over 67% and increases further as the PSA level increases.
• About 40% to 60% of men (40 to 60 men in 100) with PSA levels in this range have prostate cancer.
• A transrectal ultrasound (TRUS) and prostate biopsy are needed to confirm cancer.
• However, high levels do not always mean prostate cancer is present. PSA levels may be high if the prostate gland is
• PSA level can also be raised in:
  • benign prostatic hyperplasia, or BPH)
  • Prostatitis
• PSA levels also normally go up slowly as men age, even if there is no prostate abnormality.
• Drugs like finasteride (Proscar or Propecia) or dutasteride (Avodart) may falsely lower PSA levels.
• Some herbal preparations may also mask an elevated PSA level, but Saw palmetto (an herb used by some men to treat BPH) does not seem to interfere with the measurement of PSA.
• Since ejaculation can cause a temporary increase in blood PSA levels, patients should abstain from ejaculation for 2 days before testing.
Another method of reporting PSA levels, called percent free prostate-specific antigen (free PSA), may be used to help predict the chance that a prostate problem is noncancerous (benign) or related to cancer.
What is the free PSA test?

- Most of the PSA protein released into the blood becomes attached to other blood proteins. The PSA that does not become attached is known as free PSA and can be measured.
- It has been found that the level of free PSA is decreased in men who have prostate cancer compared to those with benign conditions.
- The exact level depends upon which test the laboratory uses, but generally less than 10% free PSA is suggestive of cancer.
- This test is most helpful when the usual PSA test is between 4 and 10 ng/mL.
• Low free PSA values (less than 15%) are more likely to be caused by prostate cancer than high free PSA values.
FALSE NEGATIVES

- Recent sexual activity or a cystoscopy test may cause prostate-specific antigen (PSA) levels to rise.
- Large doses of some medications used to treat cancer—such as cyclophosphamide (Cytoxan, Neosar), diethylstilbestrol, and methotrexate—can interfere with test results.
- The medication finasteride (Proscar), used to prevent further enlargement of the prostate gland in men with benign prostatic hypertrophy (BPH), can cause inaccurately low PSA levels.
- Rough handling, contamination, or inadequate refrigeration of the blood sample can cause inaccurate test results.
When combined with a digital rectal exam, the prostate-specific antigen (PSA) test improves the likelihood of detecting prostate cancer.

Remember: PSA levels within the normal ranges do not exclude the possibility of prostate cancer. Some men with prostate cancer have normal PSA levels.

Experts disagree about the frequency of PSA testing to screen for prostate cancer.
Since the risk for prostate cancer increases with age, it is recommended that a PSA test and DRE be performed annually for all men once they reach 50 years of age.

Men in high-risk groups, such as African Americans and those with blood relatives who have had prostate cancer, should begin testing at age 40 and consult with their health care professional for advice on more frequent testing.
Other related tests are being evaluated for their ability to distinguish between prostate cancer and benign prostatic hypertrophy.

- **The prostate-specific antigen density (PSAD) test** compares the PSA value to the size of the prostate gland. The size of the prostate is measured using transrectal ultrasound (TRUS).

- **The PSA velocity test** is a measure of how rapidly PSA levels are increasing over time. PSA levels appear to increase more rapidly over time in men with prostate cancer and more slowly in men with prostate enlargement (benign prostatic hypertrophy).
• **Complexed prostate-specific antigen (cPSA)** is a fairly new test to help detect prostate cancer.

• When used in combination with a digital rectal exam, the cPSA test is similar to the total PSA test in its ability to detect prostate cancer.

• The cPSA test currently is not widely available.
What are the limitations of the PSA test?

• A few percent of prostate cancers do not produce detectable increases in the blood PSA, even with advanced disease.

• Many early cancers will also not produce enough PSA to cause a significantly abnormal blood level.

• It is therefore important not to rely only on blood PSA testing.

• The most useful additional test is a physical prostate examination by a doctor known as the digital rectal exam (DRE).
Note: PSA is not diagnostic of cancer

Complexed PSA Test is More Accurate Than Traditional PSA Test in Detecting Prostate Cancer  
• In conclusion, prostate cancer is a common and deadly disease. **PSA, DRE, and the ultrasound-guided biopsy remain the mainstays of screening and diagnosis.**

• **Grading and staging the disease is extremely important in determining treatment.**

• **Risk factor assessment**, something we have not really thought about previously, has become increasingly important, not just to heighten our index of suspicion for individual men, but to consider preventive treatment in individuals who are at very high risk.
PROSTATE-SPECIFIC ANTIGEN (PSA)

ORGAN-SPECIFIC NOT CANCER-SPECIFIC

- PRODUCT OF PROSTATIC EPITHELIUM
  - NORMALLY SECRETED IN THE SEMEN
- VALUE AS A SCREENING TOOL IN POPULATIONS AT RISK?
  - HIGH SENSITIVITY BUT LOW SPECIFICITY !!!
    - ↑ IN BPH AND PROSTATITIS
    - SOME UNDIFFERENTIATED CaP < 4 ng/mL
- PARTICULARLY SENSITIVE AND ACCURATE FOR
  - DETECTION OF RESIDUAL CANCER
  - DETECTION OF RECURRENT CANCER
  - DETECTION OF CANCER PROGRESSION AFTER TREATMENT (i.e. RESPONSE TO THERAPY)
- SIMPLIFIED APPROACH TO SERUM PSA SCREENING IS DANGEROUS
  - DELAY IN DIAGNOSIS
  - MISSED DIAGNOSIS

CUT-OFF POINT BETWEEN NORMAL AND ABNORMAL

SERUM LEVEL > 4 ng/mL
PSA

ORGAN-SPECIFIC NOT CANCER-SPECIFIC
Healthy man  Man with prostate cancer  Missed cases

PSA suggests cancer where there is none  PSA misses these two cases  PSA finds these three cases
OTHER FACTORS THAT MAY ↑ SERUM PSA LEVELS

- BPH
- PROSTATITIS
- INSTRUMENTATION OF THE PROSTATE (e.g. TURP* FOR BPH) → PROSTATE “CHIPS”

20-40% OF PATIENTS WITH ORGAN-CONFINED CaP HAVE A PSA ≤ 4 ng/mL

*TRANS-URETHRAL RESECTION OF THE PROSTATE)
15-40% chance of undergoing a biopsy based on an abnormal screening PSA, depending on the patient’s age.
Sensitivity—85%

Specificity—91%

Area under the Receiver Operating Characteristic (ROC) curve ("Positive Predictive Value")

PSA 0.94

Mammogram 0.85

Papanicolaou smear 0.70
## “In Search of a Better (Screening) Test”

<table>
<thead>
<tr>
<th>Serum Marker</th>
<th>Cut-Off Parameters</th>
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<tbody>
<tr>
<td><strong>Total PSA</strong></td>
<td>20%-30% cancer detection rate if PSA <strong>4-10 ng/mL</strong> and normal DRE</td>
</tr>
<tr>
<td><strong>PSA velocity</strong></td>
<td>PSA velocity <strong>&gt; 0.75 ng/mL/yr</strong>, requires multiple PSA measurements over many years, biologic and assay variability bias</td>
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<tr>
<td><strong>PSA density (PSAD)</strong></td>
<td>PSAD <strong>&gt; 0.15</strong>, requires TRUS, significant decrease in biopsy numbers. Potential bias/error from ultrasound operator variability and assay variability.</td>
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<tr>
<td><strong>Age-adjusted PSA</strong></td>
<td>PSA cut-off of <strong>6.5</strong> (age &gt; 70), <strong>4.5</strong> (age 60-70), <strong>3.5</strong> (age 50-60), and <strong>2.5</strong> (age 40-50). Improved sensitivity in young men, decreased sensitivity in older men.</td>
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<tr>
<td><strong>Free/total PSA (% free PSA)</strong></td>
<td>Unnecessary biopsy reduced by 20% if % free PSA cut-off of <strong>25%</strong>. If % free PSA 0%-10% and PSA 4-10 ng/mL, cancer detection &gt; 50%.</td>
</tr>
<tr>
<td><strong>Complexed PSA</strong></td>
<td>Measurement of only 1 analyte. Reported improved specificity over total PSA. Large assay variability.</td>
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an elevated serum PSA may be a sign of prostate cancer, but it may also be a **false positive** result due to benign prostatic hyperplasia (BPH)

PSA is not very good at predicting whether the subsequent biopsy will find cancer, because **PSA is specific for the prostate but not specific for prostate cancer**

**“PSA-Dilemma” Population**

- group of men with persistently elevated serum PSA levels and at least 1 previous negative biopsy
  - *was the cancer missed on the biopsy ... or was there no cancer ???*
- these men need to undergo **repeat biopsies**
  - this incurs **costs** and carries a risk for **morbidity** as well as **emotional turmoil**, but – up until now – has been **the only way to check whether cancer is present or not**
- the alternative – “watchful waiting” with regular PSA testing – can also create anxiety and result in unnecessary medical procedures