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PROSTATE SPECIFIC ANTIGEN (PSA) EXPLANATION

WHAT IS PSA, AND HOW DO WE MEASURE IT?

PSA stands for Prostate Specific Antigen and is a blood test that is used to screen for the presence of prostate cancer.

The prostate is the gland, found only in men, which is located between the urinary bladder and the urethra (the urinary channel that runs through the penis). The prostate's function is to make seminal fluid or semen that is ejaculated during intercourse. Note that sperm is made in the testicles and is only a small fraction of the seminal fluid. Antigen is a medical or biological term for a substance, usually a protein, that stimulates the body to make antibodies.

PSA is, therefore, a protein found in the blood that is unique or specific for the prostate. No other human tissue or body part can make PSA except for the prostate. The PSA levels can be measured in an individual's serum and with this information we are able to screen for prostate cancer.

WHY USE PSA TO SCREEN FOR PROSTATE CANCER?

The routine use of PSA testing along with digital rectal examination (DRE) of the prostate has dramatically improved our ability to find prostate cancer earlier, and possibly at a more curable stage, than ever before. Controversy exists as to whether earlier diagnosis leads to longer survival, but it is our hope that PSA testing will lead to lives being saved because of earlier treatment.

WHAT CAUSES THE PSA TO RISE?

PSA is only present in men. PSA is present in all normal prostate tissue. The normal prostate cell holds onto most of the PSA and lets very little leak into the blood stream. The small amount that leaks out is the PSA that is measured by the blood test. Prostate cancer cells actually have less PSA in each cell, but the cancer cell tends to leak more PSA into the bloodstream, hence the reason for measuring the PSA levels. Knowing this fact, we have come up with a range of expected values in patients with a normal prostate gland. We believe that the PSA value should be less than 4.0. This number is somewhat arbitrary but reflects our feelings that most men (95% or so) with normal prostate glands have a PSA value of 4.0 or less (see below about age-specific normal values!). The catch is the word 'normal'. Almost any condition that affects the prostate can make the PSA rise. In addition, not all patients with prostate cancer have an elevated PSA. Twenty percent of diagnosed prostate cancers occur in men whose PSA values are normal!

The most common non-cancerous cause of elevated PSA levels is benign prostate hyperplasia, more commonly known as BPH. As men age, particularly after age 50, the prostate enlarges or grows normally. The most common symptom with BPH is difficulty urinating. About 80% of men will develop some aspect of BPH in their lifetime. BPH is NOT cancer, nor will it lead to cancer, but BPH may cause a false elevation of PSA values.

Another common cause of false elevation of PSA value is prostatitis. Prostatitis simply means inflammation of the prostate. Prostatitis is very common and usually causes symptoms similar to a

bladder infection (burning, frequency and urgency to urinate). However, many men with prostatitis have no symptoms. The inflammation from prostatitis causes PSA to leak into the bloodstream and causes the PSA level to be higher than normal. Even a simple rectal exam can cause the PSA to rise somewhat. Ejaculation has been shown to cause an increase in the PSA level in some men for about 48 hours. If possible, the patient should not ejaculate for 48 hours before a PSA test. If ejaculation has occurred and the PSA is elevated, a repeat test might be necessary. **What this means is that PSA is NOT a cancer measurement, and that an elevated PSA does NOT mean you have cancer. The ONLY test that will determine the presence of cancer with certainty is a biopsy of the prostate.**

DOES AGE HAVE ANYTHING TO DO WITH PSA LEVELS?

Recent studies have suggested that the 4.0 cut-off level may be too high for younger men and too low for older men. Most of the studies for which we have long term evaluation have used the 4.0 level. Some researchers now recommend the following levels, although more time is needed to assure that these levels are more accurate than just the 4.0 value.

Age 40-50	0 to 2.5
Age 50-60 --	0 to 3.5
Age 60-70 --	0 to 4.5
Age 70-80 --	0 to 6.5

WHAT DO WE DO WITH AN ELEVATED PSA LEVEL?

FIRST TIME MEASUREMENT OF PSA

(Note: This assumes that the rectal examination found no suspicious nodules or hardness within the gland. Even if one's PSA level is within normal range, a suspicious nodule must be evaluated.)

Remember, PSA is merely a predictor of the possibility of prostate cancer. A normal PSA does not mean that you do not have prostate cancer. It means that you have lower risk of having a prostate cancer. Conversely, an elevated PSA does not mean you have cancer either. It just means that you are at greater risk than someone whose PSA is lower.

Probability of Prostate Cancer based on test results

Standard PSA Level	Probability of Prostate Ca
0-2 ng/ml	1%
2-4 ng/ml	15%
4-10 ng/ml	25%
> 10 ng/ml	>50%

PSA of 4* or less - If your PSA level has been measured for the first time and is less than 4, we recommend repeating the test on a yearly basis.

(* this number may be dependent on age see above for normal values)

PSA greater than 4 - If your PSA is greater than 10, we recommend a diagnostic ultrasound of your prostate done through the rectum (**TransRectal Ultrasound or TRUS**) with biopsies of the prostate simultaneously. If the ultrasound shows no suspicious areas, then systematic biopsies of the entire prostate are usually taken. If the ultrasound shows suspicious areas, then biopsies of the areas, along with systematic biopsies, need to be done.

Other ways to look at PSA values (PSA Density)

Another way of looking at PSA is to measure 'PSA Density' or 'PSAD'. PSA density measures the

amount of PSA in the blood relative to the size of the prostate gland. To be exact, one divides the PSA level by the prostate size in cubic centimeters. A man with a PSA of 3.0 and a prostate estimated at 45 ccs would have a **PSAD** of 3 divided by 45 which equals 0.07. We normally expect the men with a larger non-cancerous prostate to have a higher PSA, and the smaller non-cancerous prostate glands to have a lower PSA. We become concerned about patients with PSA values out of proportion to their prostate size. Conversely, a very large prostate with a slightly high PSA might not be so suspicious by density measurements. The normal PSAD is 0.15 or less. In other words, the PSA density allows us to pick out suspicious prostate glands that could be missed by PSA levels alone. Many researchers now feel density is misleading and do not use it.

IF YOU'VE HAD PREVIOUS MEASUREMENTS OF PSA

(Note: This assumes that the rectal examination found no suspicious nodules or hardness within the gland. Even if one's PSA level is unmeasurable, a suspicious nodule must be evaluated.)

When we have the luxury of previous PSA values, we look at numbers a little bit differently. The PSA level will almost always rise in the face of a cancer that is growing. Any PSA level that is rising is suspicious. As mentioned earlier, the high PSA level may NOT mean that cancer is present. For example, a male with a stable PSA of 8 over a three year period (8,8,8) is probably at less risk than a male with a PSA of 2, 4, and 6 over the same time frame, even though the value 8 is above all the values of the second patient! The second patient's rising levels suggest growth and has to be considered suspicious for cancer. If the first patient with repeating 8 values had a negative biopsy when first discovered, then there may be no need to repeat the biopsies. If his levels jumped to 10 or 15 for no apparent reason, then repeat ultrasound and biopsies would be indicated. Recent studies suggest that either a 20% rise or a measurable rise of 0.75 in PSA in one year should prompt a closer look and possibly an ultrasound and biopsy. Some physicians use the term PSA Velocity **or** PSAV to describe the change in PSA values over time

'Free PSA' and Complexed PSA

Another new test is called 'free' PSA. Most of the PSA that circulates in the serum is usually attached to larger protein substances or 'complexed' or PSA-ACT, the rest of the PSA is unbound or 'free'. The standard PSA measurement is a reflection of all PSA, free and complexed.

$$\text{Total PSA} = \text{Free PSA} + \text{Complexed PSA}$$

Research suggests that PSA created by prostate cancer is more likely to be the 'complexed' type while non-cancerous or benign PSA is more 'free'. The percentage of free PSA to total PSA may give some additional benefits in trying to decide whom to biopsy and whom to watch. If the free PSA to total PSA is greater than 23%, cancer is more unlikely. If the percentage is less than 10%, cancer is more likely. Percentages between 10% and 23% offer no definite information. The free PSA test has been approved by the FDA, but many laboratories do not offer it and your insurance company may not pay for it (costs about \$65 at this time). The Free PSA test data is accurate for patients with PSA values between 4 and 10. The usefulness of free PSA for values below 4 and above 10 has not been established. The major value of the free PSA today is to help us decide which patients need a repeat biopsy after having a negative biopsy for elevation of the regular PSA test.

% Free PSA	Probability of Cancer
0-10%	56%
10-15%	28%
15-20%	20%
20-25%	16%
>25%	8%

Another way of evaluating the same information is the total amount of 'complexed PSA'. The normal

value for 'complexed PSA' is about 3.75 ug/ml and probably offers little benefit over total PSA.

WHAT'S NEW

We are constantly looking for better and more accurate markers. The newest is hK2 or human glandular kallikrein. hK2 is very similar to PSA and in early clinical studies using free PSA and hK2 together gave slight edge in percentages of cancers predicted, although, similar to total PSA, many more patients with elevated levels of any of these markers did NOT have cancer. Researchers are looking at a marker called PSA-AMG or alpha-2-macroglobulin (Sweden), tissue-polypeptide antigens in association with PSA (Italy), Granin-A (USA, Sweden), and PSMA or prostate specific membrane antigen (USA). Data and patient follow-up is too early to suggest any change in the-current testing methods.

Another problem, yet to be solved, is the comparison of assays for PSA, free PSA and complexed PSA. Countless companies are offering PSA test kits. Are the different kits, many of which use different chemical reactions giving the same PSA levels? The differences are probably not significant but having the PSA testing repeated at the same laboratory may be a benefit. Unfortunately, many labs change PSA testing kits without notice.

FOLLOW-UP

We agree with the American Cancer Society, the American Urological Society and other groups, that a yearly PSA along with a rectal examination of the prostate should be offered to men over age 50. In high risk groups, such as African-American men and men with a family history of prostate cancer, screening should start at age 40. Given a normal, and stable PSA, we firmly believe that routine ultrasound of the prostate is not indicated.

We also recognize that many groups feel that PSA screening should not be done routinely. To date, no evidence exists that routine PSA screening saves lives and many believe that the treatment of prostate cancer might cause more harm than help. Patients need to be aware of the risks of screening and not screening. Please ask if you have any questions,

Glossary of terms - Acronyms or Abbreviations

PSA: Prostate Specific Antigen

PSAD: Prostate Specific Antigen Density

PSAV: Prostate Specific Antigen Velocity

DRE: Digital Rectal Examination

TRUS: Trans Rectal UltraSound