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DIAGNOSTICS: The Pca3 Urine Test - Increasing Applications

The PCA3 urine test measures PCA3 (Prostate Cancer Antigen 3) gene expression and has gained acceptance among urologists because of its high specificity for identifying prostate cancer, for estimating prostate cancer volume, predicting the likelihood of extracapsular tumor extension, and indicating the likelihood that a repeat biopsy will show cancer after an initial negative biopsy. Test kits are generally available in urologists' offices and the 2cc of urine following a mild prostatic massage are sent to the Bostwick Lab for analysis. (For information call Bonnie Scott at 206-853-2573.) An article in the November 2007 PCa Commentary described the biology underlying the test: "PCA3 Molecular Urine Assay for Prostate Cancer in Men Undergoing Repeat Biopsy", indexed under "Diagnostics."

Sufficient experience with the test's performance has allowed Drs. Leonard Marks and David Bostwick (of Bostwick Labs) to summarize outcome data of the PCA3 test in its various applications: "Prostate Cancer Specificity of PCA3 Gene Testing: Examples from Clinical Practice, Reviews in Urology, Summer 2008. Bostwick states that the PCA3 gene "is the most specific prostate cancer gene identified to date" for indicating early prostate cancer. "PCA3 transcripts have not been detected in a wide range of human extraprostatic benign and cancerous tissues." Unlike the protein PSA, which is secreted into the serum, the PCA3 urine test targets messenger PCA3 RNA in the post-massage cellular-rich fluid. PCA3 mRNA emanates from the nucleus of prostate cancer cells where it is expressed 60- to 100-fold compared to the level of expression in benign prostate tissue. It is this marked over-expression in

malignant cells that facilitates the identification of prostate cancer by using the quantification of cellular bound PCA3 mRNA as a surrogate for the presence and extent of cancer relative to benign prostate cells. As this ratio (the score) increases it first points to the presence of cancer, then to greater cancer volume, and even higher ratios point to extracapsular extension. The Bostwick Lab has found that a cut-off threshold value of a ratio of 35 offers the optimal balance of specificity and sensitivity.

What clinical distinctions can purportedly be established from a score greater than 35 - especially from an increasingly higher score?

1) PCA3 test values >35 predict a biopsy diagnosis of prostate cancer with a specificity of 74% and a sensitivity of 54% [see Ellis below], which is superior to the accuracy of the PSA test. The probability of a cancer diagnosis increases with the PCA3 score. An excellent article authored, among others, by Drs. Bill Ellis and Alan Partin (J.Urol Apr 2008) is a very informative primer for practitioners beginning to use this test. The study was based on 570 men, slightly skewed toward higher risk disease, who were scheduled for first and repeat biopsies. "Men with a PCA3 score of less than 5 showed a positive biopsy rate of 14%, whereas with a PCA3 score of greater than 100 69% were biopsy positive," and the "diagnostic accuracy does not depend on whether the individual has an initial or repeat biopsy." Histologies of PIN or ASAP alone or combined led to slight increases in median PCA3 scores in the range of 23 to 27. The PCA3 score was independent of the volume of the total prostate gland. These authors and other researchers are investigating the potential of improved diagnostic accuracy through synergism of the PCA3 test with more traditional parameters

   Corollary to the basic information presented above three generalizations follow:

   a) A likelihood can be estimated that a man with a high serum PSA value coupled with a low PCA3 score results from BPH and not from significant cancer;

   b) Since prostate inflammation does not increase the mPCA3 transcripts, a high PSA resulting from prostatitis can be distinguished from significant cancer; and,

   c) After a negative initial biopsy performed because of appropriate clinical indications, a PCA3 value of >35 can be informative in predicting the likelihood that a repeat biopsy will show cancer.

2) An increasing PCA3 value was found "significantly correlated with the total cancer volume, p =<0.01, as opposed to total prostate volume. (MCleod, Sirvatava, et al., J.Urol, Sept, 2008)

   a) Serial measurements using the PCA3 test in one study suggested promise as a means of selecting and following men on a protocol of active surveillance: "The PCA3 score was significantly different when comparing low volume/low grade (dominant tumor volume less than 0.5 cc, Gleason score 6) and significant cancer (p =0.007). (Nakanishi, J.Urol, May 2008)

3) McLeod (J.Urol, Sept, 2008) found "At a cutoff PCA3 score of 47 extracapsular extension (ECE) was predicted with 94% specificity and an 80% positive predictive value. In their study the [median] score for those with ECE was 48.8 vs 18.7 for those men without ECE, p =0.01".

The list price of the test is $450 and the test cost is covered by Medicare, Medicaid, and all insurance plans. As with any relatively new test, there is a need for further validation, but studies to date of the PCA3 urine test already have shown predictive potential, and combinations of the PCA3 urine test with traditional predictors promise even further diagnostic accuracy.

CLINICAL TRIALS: Canary Prostate Active Surveillance Study (PASS) Is Open For Registration

Dr. Dan Lin is the principle investigator for this protocol at the University of Washington. The study is sponsored nationally by the Canary Foundation and NCI/Early detection Research Network. The schema was described in the June PCa Commentary (indexed under "Clinical Trials") and detailed information is available at http://www.clinicaltrials.gov/ct2/show/NCT00756665.

The purpose of the trial: "The Prostate Active Surveillance Study (PASS) is a research study for men who have chosen active surveillance as a management plan for their prostate cancer. Active surveillance is defined as close monitoring of prostate cancer with the offer of treatment if there are changes in test results. This study seeks to discover markers that will identify cancers that are more aggressive from those tumors that grow slowly."

A brief description: "This is a multi-center, prospective active surveillance study with selective intervention in patients with previously untreated, clinically localized prostate cancer at diagnosis. Candidates are assessed based on an extended core biopsy, serum PSA (including PSA kinetics, if available), digital rectal examination (DRE), and assessment of cancer grade and extent."

For more information about the trial and for patient registration call Lisa Newcomb at the University of Washington, 206-667-1946, or Sharon Downing, RN, at 206-598-0850, or e-mail at sdowning@u.washington.edu.

HORMONE INTERVENTION: Clinical Briefs

Antiandrogen Withdrawal:

1) "Antiandrogen Withdrawal in Castrate-refractory Prostate Cancer," SWOG Trial 9426 (CANCER, June 1, 2008).

   A prospective multi-institutional study of 210 men showed that 21% had confirmed PSA decreases of ≥50% upon antiandrogen withdrawal following PSA increases (≥ 4 ng/ml) during treatment with combined androgen blockade (CAB). The overall median progression-free survival (PFS) was 3 months, although "19% had 12-month or greater progression-free intervals." The median overall survival for men with PSA progression only was 40 months, and was 20 months for those with evidence of bone metastases. Longer duration of antiandrogen usage, a lower PSA at baseline, and PSA only progression were associated with a longer PFS. Because of its long half-life, response to bicalutamide may not be evident for 6 to 8 weeks.

2) "Alternative nonsteroidal antiandrogen therapy for advanced prostate cancer that relapsed after initial maximum androgen blockade," J.Urol,Sept 2008).

   This article builds on the summary above and confirms that a response to initial antiandrogen withdrawal following PSA relapse during CAB predicts for a response to secondary hormone therapy and finds that even a partial response has clinical benefit. Of the 232 men in this Japanese study with advanced prostate cancer (mean baseline PSA 1047 ng/ml; 75% with M1 disease), 15.5% showed a ≥50 decrease in PSA following withdrawal of bicalutamide (80 mg/d), and 12.8% after flutamide (375 mg/d), (no statistical difference).

   Cause specific survival (CSS) was significantly prolonged in the those who achieved an initial PSA nadir of <4 ng/ml from initial combined therapy, and was further lengthened in those men who also experienced a withdrawal response, as compared to men not responding to withdrawal. A notable

finding was that the 25.4% patients who had only a partial withdrawal response following initial CAB relapse (i.e. stable PSA to 25% decrease) gained a benefit in CSS compared to those with no withdrawal response, p<0.005.

The response rate (≥50% PSA decline) to second line hormone therapy was 35.8% with both alternate drugs performing equally, and a second response significantly increased CSS. "Significant clinical factors that predicted the response to second line therapy were clinical stage, M category, and the response to first line CAB therapy."

Testosterone Recovery Following Androgen Suppression:

1) Short Term Androgen Suppression (AS): Many studies have addressed testosterone recovery following a single administration of "3 month" Lupron. A typical finding was that the majority of men only rise above a T level of 50 ng/mL 6 months after the shot. [Discussed in June 2006 and September 2007 in PCa Commentary indexed under "Hormone Intervention.]

2) Timing of Testosterone Recovery Following 6 Month Androgen Suppression.

   Gully and Dahut et al. found in a study of 129 men (non-metastatic prostate cancer and a rising PSA to >5ng/ml) that T normalized in 15.4 weeks following a first cycle of two 3-month Lupron administrations, and after a second 6 month cycle given upon PSA recovery, the T normalized in a median of 18.3 weeks. The interval was measured from the date of the second Lupron shot in each cycle. The "normal" T level was set at 212 ng/dl. Men older than 67 years or those who had subnormal baseline T levels attained T normalization at 22.4 weeks vs. 13.2 weeks for younger men. Twenty seven of 128 men did not recover normal T production following the first cycle.

   Partial recovery to supracastrate levels of testosterone of >20ng/dl but <212ng/dl was analyzed, and this data may be useful in planning strategies of intermittent androgen suppression. For those 94 of 128 (72%) men who achieved a T nadir of <20 ng/dl recovery of T into the 50 to 211 ng/dl range occurred by 12.8 weeks compared to 6.7 weeks for those with a higher T nadir.

   Following the second cycle T normalization occurred in a median time of 18.3 weeks. The "overall median time to an increase in T to low levels was 11.5 weeks." There was a trend of longer times to T normalization in men who had received radiation therapy. Dihydrotestosterone levels closely followed the recovery pattern of testosterone.

3) Testosterone Recovery after 2 Years of AS: Longer periods of androgen suppression are associated with longer times to testosterone recovery. Choo, Yoon et al. documented this recognized pattern (J.Urol,Oct, 2008) based on a Mayo Clinic study of 141 men following surgery (pT3N0M0 or positive margins) who received 2 years of androgen suppression following initial treatment with radiation to the prostate. All men achieved T nadir levels of 50 ng/dl or less from AS. Their findings "suggest that it takes a median of 22.3 months for testosterone levels to recovery to baseline and/or normal levels in men who have received 2 years of AS." Men younger than 60 years recovered faster than older men, i.e. median of 16.4 months vs. 28 months, respectively. Testosterone recovery to levels greater than 50 ng/dl took a median of about 12 months and was not influenced by age.

   Editorial Comment: Androgen suppression casts and long and variable shadow as testosterone levels slowly return to normal, or near normal pretreatment levels. The length of suppression is largely dependent upon the duration of AS therapy, the patient's age, pretreatment testosterone level, and the depth of the PSA nadir after the initiation of AS therapy. Information about this duration of hypogonadism is useful in counseling patients about the expected duration of symptoms, the interpretation of clinical trial data, and for planning regimens of intermittent androgen

suppression. An editorial comment following the Gully article stated: "Clinicians should consider measuring serum T at the pretreatment baseline and after the cessation of an LHRH analogue."

DIAGNOSTICS: Two New On-Line Calculators And An Up-Date Of An Older Standard

Two new on-line calculators are now available for risk assessment.

Ian Thompson, et al. based a new calculator on The Prostate Cancer Prevention Trial data and suggested the thrust of their analysis in their title, "It's Time to Abandon an Upper Limit of Normal for Prostate Specific Antigen: Assessing the Risk of Prostate Cancer," (J.Urol, Oct. 2008). Their calculator integrates 6 factors: PSA, age, race, family history, DRE status, and history of prior negative prostate biopsy. The impetus for their work was to better identify the 15% of the 2950 men in the placebo arm of the trial who had PSA values of <2.5 ng/mL and were diagnosed with cancer, of whom 15% showed Gleason score 7 to 10. The calculator is found at http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp

The second calculator is an ambitious project led by Matthew Katz, Saints Medical Center, Lowell, Mass, and was presented as abstract #88 at the recent ASTRO meeting. The on-line calculator is found at www.capcalculator.org, and requires a brief registration to gain access. The strength of the product is its integration of information from "peer-reviewed, published articles about risk-assessment tools for predicting pathologic stage and treatment outcomes in men with clinical T1-3 prostate cancer." The incorporated factors include: patient age, clinical T stage, final Gleason score, total number of cores taken and the number positive (including Gleason grade data on positive cores and percentage of cancer in those cores), and radiation dose of EBRT and BT.

The calculator presents estimates for the extent of disease to be found at surgery, and estimates PSA outcome (freedom from PSA relapse) at 5 and 10 years following treatment with RP, EBRT and BT; and estimates clinical outcome after EBRT, but not after radical prostatectomy or BT. This calculator is no doubt a work in progress with additional information to be added, and it notably lacks significant brachytherapy outcomes such as data from the Seattle Prostate Institute

The weakness and strength of incorporating data from multiple sources is that for each category there is an unsettlingly wide range of outcome estimates, but this may at the same time serve as a useful reminder that all estimates are, well, in fact only estimates.

The venerable prostate risk calculator from the Memorial Sloan-Kettering Cancer Center remains available at http://www.mskcc.org/mskcc/html/10088.cfm. The entry data has been expanded to include information about number of biopsy cores positive, and outcome data has been updated. Currently it is more informative than the Katz product. As before, the MSKCC tool gives information in four areas: 1) pre-treatment estimates of pathology and outcome for RP, EBRT, and BT; 2) outcome data based on surgical pathology; 3) outcome from salvage radiotherapy; and 4) survival estimates for men who are hormone refractory.