Best of the 1999 AUA Annual Meeting

Highlights from the American Urological Association Annual Meeting
May 1-6, 1999, Dallas, Texas

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The 1999 AUA Annual Meeting in Dallas was packed with practical information. Here, Contributing Editors of *Reviews in Urology* and associates describe outstanding contributions they feel merit special attention.

Key words
Prostate specific antigen (PSA) • Incontinence, urinary • Carcinoma, transitional cell • Reflux, vesicoureteral • Benign prostatic hyperplasia (BPH) • Ultrasonography • Prostatectomy • Erectile dysfunction • Growth factors • Human kallikrein

Main Points

- Some researchers are suggesting an interval of 2 years starting at age 40 when testing for prostate cancer, to reduce the number of deaths, PSA tests, and biopsies.
- Cessation of antibiotics in carefully selected children with persistent reflux can be safe.
- A strong relationship exists between serum PSA and prostate volume in men with BPH.
- In men who have an undetectable serum PSA level following retropubic prostatectomy, serial DRE or imaging studies may not be needed.
- A new technology for analyzing multivariable data sets (neural network) may be able to predict biochemical (PSA) recurrence following radical prostatectomy.
- In a screening population, cPSA seems to provide better stratifying information for prostate cancer when tPSAs are lower (4-6 ng/mL); f/tPSA ratio seems to give better information with higher tPSAs (6-8 ng/mL).
- A national standard for tPSA and fPSA is needed.

Prostate Cancer Screening

Controversy regarding the necessity for screening or early detection for prostate cancer stems from many sources. Arguments against prostate cancer screening include lack of documented proof of decrease in cancer mortality, fear of increased detection of insignificant cancers, unnecessary anxiety for those being screened, and the major impact on the cost of medical care that is required for prostate specific antigen (PSA) screening. Investigators at Johns Hopkins Hospital in collaboration with biostatisticians and epidemiologists at Merck, Inc, investigated the impact of different PSA screening strategies on prostate cancer detection and mortality.

These investigators developed a computer simulation of the natural history of prostate cancer progression in a population.[1] From these simulations, they were able to test the effect of various testing intervals, age ranges, and PSA cutoffs for prostate cancer screening. The information used for this study was taken from the Surveillance, Epidemiology, and End-Result (SEER) database, from Homestead County community population data, and from a large surgical series of men treated for prostate cancer.

In this study, all men were classified as being without prostate cancer, having insignificant prostate cancer, having organ-confined significant prostate cancer, or having significant prostate cancer that was no longer confined to the prostate. The decision as to curability was based on disease confined to the prostate. Using these simulations, prostate cancer death rates for various testing intervals varied between 5.8 and 7.5 prostate cancer deaths per 1,000. The number of biopsies needed to detect curable cancer also varied between 4.2 and 16.7 biopsies per curable cancer detected.

Compared with our present strategy for annual testing with PSA and digital rectal examination (DRE) for men starting at age 50 (AUA and American Cancer Society recommendation), these investigators demonstrated that if PSA testing were initiated at age 45, it would reduce prostate cancer deaths by 0.7 per 1,000 men tested at a cost of approximately 4,700 more PSA tests and 18 more biopsies in this simulated population. Therefore, simply lowering the age for PSA screening is not recommended from this

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study. The strategy demonstrated by these authors that reduced prostate cancer deaths, the number of PSA tests needed, and the number of biopsies that needed to be performed for detecting curable cancer was a testing interval of 2 years starting at age 40. This screening strategy decreased prostate cancer deaths by 0.2 per 1,000, decreased the number of PSA tests needed by 5,800, and required 266 fewer biopsies in this simulated population. It is also important to note that these authors found lowering the PSA cutoff to 3.0 or 2.5 ng/mL did not prevent more cancer deaths but doubled or tripled the number of biopsies needed to find curable prostate cancer.

This computer simulation represents a very clear analysis of our present PSA screening strategy for the detection of curable prostate cancer and offers some preliminary suggestions as to how we might optimize our method for detecting prostate cancer. Prospective validation of this proposed strategy would, of course, take many years to document. However, validation from other databases may demonstrate the importance and clinical utility of these very interesting findings. [Dr. Partin]

Neurogenic Bladder and Urinary Incontinence

Urology, along with all specialties of medicine, is, I believe, on the brink of a revolution. This revolution is called molecular medicine. While traditional medicine treats symptoms, gene therapy addresses the deficiency that causes the symptoms. With our rapidly improving understanding of the human genome and how to construct gene therapy vectors to manipulate our genetics, we will change the way we practice medicine forever.

Drug delivery technologies will allow us to get the drug or a gene to a specific target organ and thus limit side effects. Through gene therapy, we will replace, supplement, or suppress a protein or cytokine to correct a disease process. Gene therapy in urology may not be that far away.

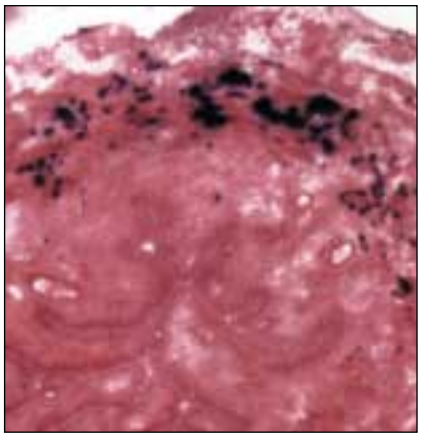

Figure 1. HSV vector-mediated ß-galactosidase expression localized to bladder smooth muscle, demonstrating survival and viability of HSV in the bladder wall nerve fibers. Photomicrograph (10x) of bladder 4 days after injection of HSV vector that, in addition to expressing NGF, also expresses the ß-galactosidase reporter gene. Pink areas: cross-section of the bladder wall with urothelium on the bottom (hematoxylin-eosin staining); dark blue: LacZ staining of HSV expressing ß-galactosidase.

An abstract from Yoshimura and colleagues is the first report of non-cancer-related gene therapy in the bladder that demonstrated physiologic improvement.[2] I am proud to be a member of this research team. The work described in the abstract had high impact and was well recognized at the AUA meeting. The work won virtually all the prizes in the field of neurourology and urinary incontinence including the Grand Prize Winner of the International Jack Lapides Essay Contest on Urodynamic and Neuro-urology Research, the Urodynamic Society's 20th Annual Meeting Best Poster Essay Contest, and the 94th American Urological Association Annual Meeting Best Poster Contest in Urinary Incontinence.

The study addresses one of the most challenging problems in all of neurourology—the diabetic neurogenic bladder. Diabetic cystopathy is a common problem with no good treatment options. Many diabetic patients will develop a sensory neurogenic bladder within 10 years of disease onset. The symptoms include progressive decreasing bladder sensation and increasing bladder capacity. The end result is a large and acontractile bladder. Patients with this condition are treated by catheterization. There are no medical treatment options for diabetic sensory neuropathy.

In a rat model of diabetic cystopathy, the investigators injected into the bladder wall with a specially constructed nonreplicating human simplex virus (HSV) vector. This recombinant herpes vector mediates the expression of ß-nerve growth factor (ß-NGF). NGF is a neurotrophic factor that, in experimental conditions, has been shown to prevent and reverse diabetic neuropathy. Using the safe nonreplicating, latent HSV vector, we can express NGF not only in the bladder (Figure 1) but also in the dorsal root ganglion of the pelvic nerve. We have exciting data suggesting that expression of NGF in the bladder and dorsal root ganglia can prevent diabetic cystopathy.

This animal work is obviously preliminary. However, we hope the readers of *Reviews in Urology* will gain insight into the potential this type of research offers. This form of treatment will not be available today or tomorrow, but perhaps it is not as far away as it once seemed. [Dr. Chancellor]

Minimally Invasive Surgery

Endoscopic diagnosis and management of transitional cell carcinoma (TCC) is standard in the lower urinary tract, especially for disease with a low grade and stage. With improvements in instrumentation and technical refinements, urothelial lesions in the upper urinary tract can not only be diagnosed endoscopically, but patients can also often be treated using this technique.

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One study reviewed the usefulness of surveillance modalities in those patients with prior ureteroscopically resected TCC.[3] Ureteroscopy was the gold standard in diagnosing urothelial recurrence as compared with retrograde contrast radiography and cytology.

Endoscopic treatment of patients with upper urinary tract TCC and normal contralateral renal units was also an area of study.[4] As in other published series, the majority (81% in this study) of upper tract TCC was of low grade and low stage. These lesions did not progress after endoscopic management with either holmium or Nd:YAG laser energy. Thirty-eight percent of these lesions did recur during follow-up with a similar stage and grade as the primary ureteral tumor. This is similar to recurrence rates for low grade, low stage lesions of the bladder. The authors emphasized the importance of close endoscopic surveillance after initial ureteroscopic treatment.

In summary, these 2 presentations underscored the usefulness of retrograde ureteropyeloscopy in the management of upper urinary tract TCC. It is an essential component of the initial diagnostic algorithm. Additionally, it is useful in treating select patients with low grade, low stage lesions who are willing to follow a careful program of serial endoscopic examinations. [Dr. Grasso]

Reflux in Children

We are often asked by parents of older children with persistent reflux: "When can my child stop taking antibiotics?" Chung and colleagues from the Children's Hospital in Philadelphia presented their 14-year experience addressing the issue of terminating antibiotic prophylaxis in this setting.[5] The 48 children (38 girls, average age 9.2 years; 10 boys, average age 6.1 years) in the study were felt to be at low risk for pyelonephritis, had normal voiding patterns, and had no upper tract scarring. The average grade of reflux at presentation was grade III. All of these children were capable of indicating that they were experiencing symptoms if they developed a urinary tract infection. Most of the children did not have a history of recurrent infection. Renal sonogram and radionuclide cystourethrography were performed annually until the reflux resolved. Follow-up was for an average of 3.6 years. Seventy-nine percent of the children had persistent reflux while, in the remainder, reflux resolved on an average of 4.4 years after discontinuing antibiotics, by an average of ~12 years of age. Within about 2.3 years after the cessation of antibiotics, 5 girls and 1 boy (12.5%) developed a urinary tract infection. Of these 6 children, 5 had a febrile infection. Following oral antibiotic therapy, these 5 patients underwent ureteral reimplantation. No new scarring was noted on follow-up ultrasound studies. These authors appropriately concluded that the cessation of antibiotics in children with persistent reflux can be safe. The population in which this is performed should be carefully selected to assure the best outcome. [Dr. Shapiro]

PSA, Prostate Volume, and BPH

It has recently been suggested that the outcomes of medical treatment for benign prostatic hyperplasia (BPH) with the 5α-reductase inhibitor finasteride (Proscar®) depend to some degree on the prostatic volume at baseline.[6] However, the clinical utility of this finding has been limited by the ability of physicians to accurately predict degrees of prostate enlargement by DRE.[7] Knowing there is a relationship between patient age and prostate volume as well as a relationship between patient age and serum PSA, it appeared reasonable to investigate a possible relationship between serum PSA and prostate volume in men with BPH to determine whether serum PSA might be a useful proxy parameter to predict degrees of prostatic enlargement.

The first large-scale analysis of this kind was published recently.[8] In this analysis, baseline data from over 4400 patients ranging in age from <30 years to >70 years were pooled to study the relationship between serum PSA and prostate volume. Of note, all patients were screened and prostate cancer was excluded to the largest extent possible. All prostate volume measurements were done by either transrectal ultrasonography (TRUS) or magnetic resonance imaging. In addition, all serum PSA measurements were done in a central laboratory by the Hybritech method. The findings of this analysis were a log-linear relationship between serum PSA and prostate volume influenced by patient age. For example, the increase in prostate volume per unit of serum PSA was greater for men in their 70s than for men in their 60s and 50s, respectively. If one wished to achieve a specificity of 70% while maintaining a sensitivity between 65% and 70%, the age-specific criteria for detecting men whose prostate glands exceeded 40 mL were PSA levels of >1.6 ng/mL, >2.0 ng/mL, and >2.3 ng/mL for men with BPH in their 50s, 60s, and 70s, respectively.

Four abstracts presented during the 1999 AUA Meeting addressed this topic in large data sets derived from various sources. While some of the differences in the findings reported may be due to the inhomogeneity of the populations studied, overall a surprisingly coherent message emerges—namely, that of a strong relationship between serum PSA and prostate volume in men with BPH that will be of considerable clinical utility.

Girman and colleagues examined data from 4 different sources: the Olmsted County Study of Urinary Symptoms and Health Status Among Men (n=471), a community study in Scotland involving over 800 patients,

baseline data from the VA Cooperative Study (n=1222) from 31 centers, and a series of 100 men from a urology clinic examined by a single investigator.[9] In all studies, serum PSA and TRUS measured volume were significantly correlated (correlation coefficient, r=0.53 to 0.64). These investigators found that PSA accounted for 30% to 40% of the variability in prostate volume in the various studies. According to receiver operator characteristic (ROC) curves, PSA showed a 76% to 83% chance of correctly classifying men with prostate volumes over 30 mL, and a 76% to 83% chance of correctly classifying men with prostate volumes over 40 mL.

Hochberg and colleagues examined the relationship between serum PSA and TRUS volume in 1950 patients who were referred for an elevated PSA or suspicious DRE, who underwent a TRUS-guided biopsy, and who were found to have histologically confirmed BPH.[10] In this data set, the authors found a log-linear relationship between serum PSA and prostate volume with a correlation coefficient of r=0.39 (P<0.05).

Baseline data were presented for 3047 men enrolled in the MTOPS (Medical Therapy for Prostatic Symptoms) multicenter trial sponsored by the National Institutes of Health.[11] These men, enrolled in 17 academic centers across the United States, had to have lower urinary tract symptoms (LUTS) suggestive of BPH, had to be over the age of 50, and had to have a peak flow rate between 4 and 15 mL with an American Urological Association Symptom Score of >8 points. Prostate cancer was excluded by clinical criteria and, in addition, 39.4% of the patients participated in a biopsy substudy and underwent at baseline a TRUS-guided biopsy. All patients underwent at baseline TRUS measurement of the total prostate volume (TPV) and the transition zone volume (TZV) by the prolate ellipsoid method as well as serum PSA measurement in a central laboratory. The patients' mean age at baseline was 62.6 years with a range from 50 to 89 years, and their serum PSA was 2.4 ng/mL with a range from 0.2 to 10.55 ng/mL.

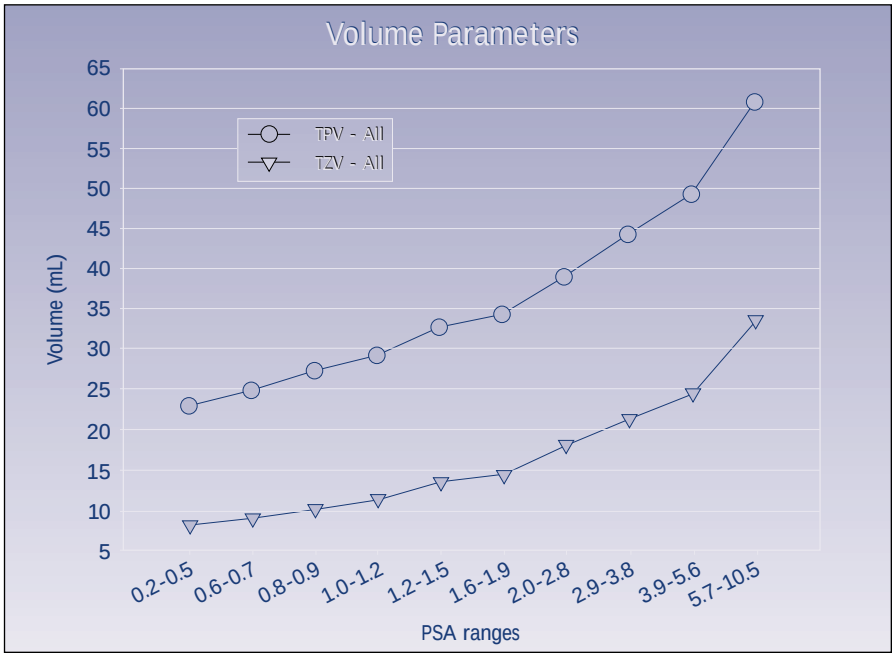

Figure 2. Mean values for volume parameters stratified by PSA ranges (deciles).

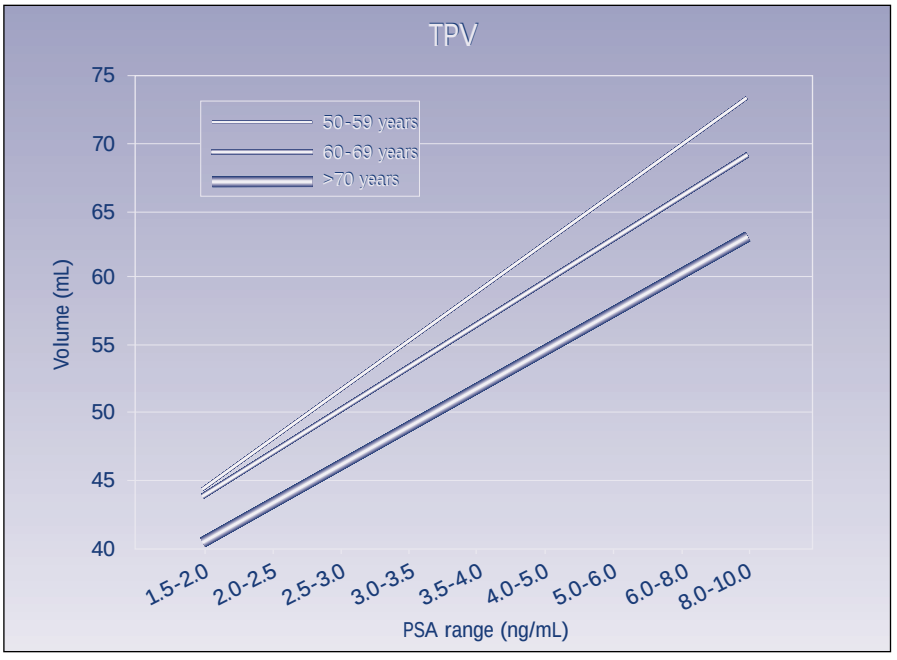

Figure 3A. TPV stratified by PSA ranges. All patients are stratified by age, and there is linear regression for each age stratum.

TRUS measured TPV was 36.3 (range, 6.1 to 185.0) mL, and TZV was 16.4 (range, 0.9 to 161.0) mL. The Spearman correlation coefficients were r=0.59 and 0.56 for the relationship between serum PSA and TPV

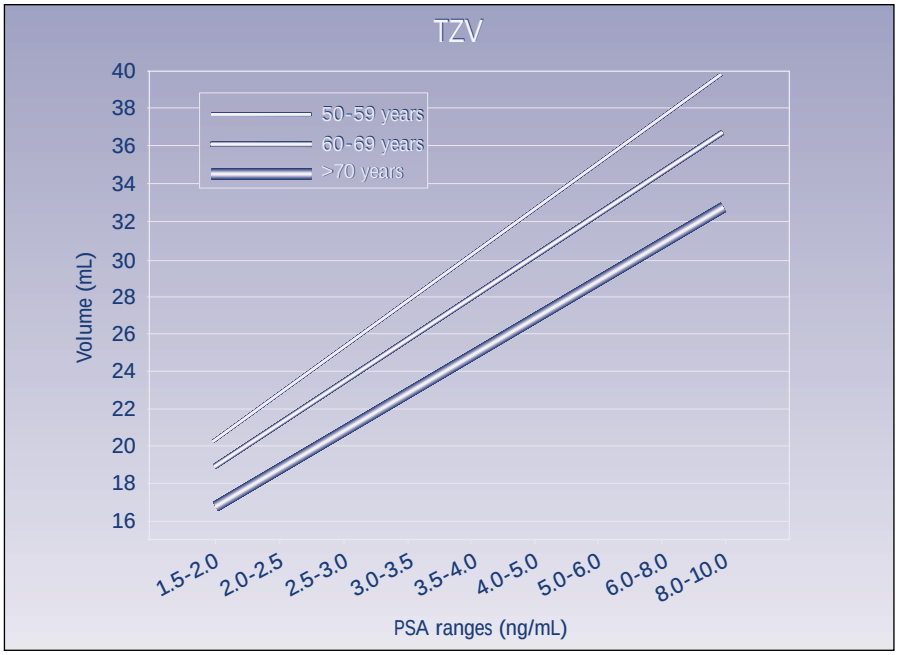

Figure 3B. TZV stratified by PSA ranges. All patients are stratified by age, and there is linear regression for each age stratum.

and TZV, respectively. The correlation coefficients for the relationship between age and other parameters were r=0.24 (PSA), r=0.25 (TPV), and r=0.25 (TZV). When stratifying the total population by deciles of serum PSA and calculating the mean values for both TPV and TZV, a clear relationship emerges between serum PSA and an increase in prostate volume measures. In fact, the increase in TPV is paralleled by an increase in TZV, implying that the overall volume increase with increasing serum PSA is, to the largest degree, due to an increase in TZV with a relatively stable peripheral zone volume (Figure 2). Accepting a false-positive rate of 30%, PSA cut points of >1.4, >1.6, and >1.8 ng/mL can be used to predict a degree of prostatic enlargement above a threshold of 30 mL for men in their 50s, 60s, and 70s, respectively. To predict a degree of prostatic enlargement of >40 mL, the cut points are >1.7, >2.0, and >2.3 ng/mL, respectively.

Baseline data from a large multicenter trial comparing the safety and efficacy of a new dual inhibitor of both 5α-reductase isoenzymes (Dutasteride) with placebo in 2800 men (ARIA 3001/3002) were analyzed in a similar fashion.[12] In these studies, only patients with a serum PSA at baseline of ≥1.5 ng/mL and <10 ng/mL as well as a TPV measured by TRUS of ≥30 mL were allowed to participate. At baseline, mean patient age was 66.4 years, and mean serum PSA was 3.9 ng/mL. TPV was 54.6 mL, and TZV was 26.8 mL. Correlation coefficients were calculated and found to be r=0.38 and r=0.35 for the relationship between serum PSA and TPV and TZV, respectively. Figures 3A and 3B show linear regression for men in their 50s, 60s, and 70s, for the mean TPV and TZV for all patients stratified by PSA ranges. From these data, a nearly linear relationship between serum PSA and TPV and TZV, influenced by patient age in the same fashion as discussed above, is evident.

Data are now available on over 10,000 men, mostly with LUTS and clinical BPH, for whom relationships between serum PSA and either total and/or TZV of the prostate has been established after clinical exclusion of prostate cancer. It is clear from these data that, across a wide variety of data sources, a clinically useful relationship between serum PSA and prostate volume can be gleaned, allowing the calculation of PSA cut points to detect certain degrees of prostatic enlargement that may be relevant from either a diagnostic or therapeutic point of view. [Dr. Roehrborn]

Localized Prostate Cancer

Many exciting new discoveries pertaining to localized prostate cancer were discussed at the AUA annual meeting, with a total of 144 papers presented in this area alone. Following are highlights of 9 of these scientifically exciting and clinically relevant studies.

The morbidity of radical retropubic prostatectomy has been a controversial and widely discussed topic in both the academic and lay literature. Several techniques for improving postoperative potency and urinary continence rates have been recommended. A previous report[13] suggested that preservation of the bladder neck during radical retropubic prostatectomy could increase overall urinary continence rates following surgery. Marcovich and coworkers from the University of Michigan[14] examined the role of this bladder-neck-sparing (BNS) modification of radical retropubic prostatectomy in affecting the likelihood of positive surgical margins and cancer recurrence. The authors evaluated 752 consecutive men undergoing radical prostatectomy, of which 222 had undergone BNS surgery. In attempting to avoid selection bias, Marcovich and colleagues stratified and evaluated these men by pathologic stage, preoperative serum PSA, and Gleason score. When stratified by pathologic stage, pT3a tumors in men who had undergone BNS surgery had a signif-

icantly higher rate of positive surgical margins than pT3a tumors in the standard retropubic prostatectomy cohort. There was also a trend toward increased biochemical recurrence rates associated with BNS surgery. This paper brings to light the importance of maintaining the efficacy of cancer control in any technical change in the practice of radical prostatectomy designed to decrease morbidity. Several other studies presented at the AUA (not reviewed) documented similar results. The definitive answer to this question awaits a multi-institutional, prospective, patient-blinded comparison of BNS and standard techniques.

Sildenafil (Viagra®) has been available to patients for treatment of erectile dysfunction following definitive therapy (radiation or surgery) for prostate cancer for well over a year now, with several investigators reporting promising results with this medication after radical retropubic prostatectomy. Zagaja and associates[15] retrospectively surveyed 150 men who had not spontaneously recovered erections sufficient for intercourse after radical retropubic prostatectomy and had subsequently received sildenafil. Patient reported data was gathered by a confidential mail survey. The authors demonstrated an age-related response to the use of sildenafil in this group of men. No patient over age 70 years, independent of neurovascular bundle status, demonstrated an adequate erection after sildenafil therapy. One year after surgery, 83% of the patients who had both neurovascular bundles preserved and who were 46 to 55 years old had erections adequate for intercourse. Similar to previous reports, these investigators demonstrated that bilateral nerve sparing improves the response to sildenafil when compared with unilateral and nonnerve-sparing surgery. These results confirm the preliminary reports of other investigators and highlight the need for nerve sparing during a radical retropubic prostatectomy if postoperative improvement in potency rates is to be achieved with sildenafil. These results also confirm the pathophysiology and pharmacology underlying the effectiveness of this agent. Similar studies (not reviewed) have documented a similar response to sildenafil following primary radiation therapy for localized prostate cancer.

Previously reported studies have identified wide variability in the rates of recovery of potency and urinary continence following radical retropubic prostatectomy. Patient selection, comorbidity, surgical technique, and, most importantly, the means of acquiring outcomes data (patient reported versus physician acquired) have been cited as reasons for this enormous variability. Walsh and colleagues[16] from the Johns Hopkins Hospital prospectively studied 70 preoperatively potent patients with clinically localized prostate cancer who underwent anatomic radical retropubic prostatectomy. In this study, 89% of the men underwent bilateral nerve-sparing surgery, 82% demonstrated organ-confined disease, and 2% had positive surgical margins. Patients completed the UCLA Prostate Cancer Index, a validated questionnaire assessing urinary and sexual function, prior to and 3, 6, and 12 months following surgery. The questionnaires were independently evaluated by a member of the research team with no knowledge of the patients' surgical or clinical history. Physician reported outcomes were assessed per the standard practice of the attending physician. Patient reported and physician reported outcomes for potency were concordant 92% of the time. For continence, 97% of the patient and physician reported outcomes were consistent. One year after surgery, there was total consistency between physician reported and patient reported potency and continence rates. This is the first study documenting that carefully recorded physician outcomes correlate well with patient reported outcomes with respect to continence and potency after radical prostatectomy. These findings should assist us in our understanding of the differences between reported morbidity rates in retropubic prostatectomy series. The results offer reassurance that, when asked in an informed and sensitive fashion, patients are forthcoming and honest in reporting potency and urinary continence outcomes to their surgeon.

Local or distant prostate cancer recurrence after radical prostatectomy in the absence of a detectable serum PSA level has been reported only anecdotally. Pound and colleagues[17] investigated the clinical course of over 1,900 consecutive men treated over a 14-year period with radical prostatectomy to document the true incidence of cancer recurrence with an undetectable PSA level. With over 10,000 patient-years of follow-up, no man developed either a local recurrence or distant metastases in the absence of a detectable serum PSA level. The authors also documented that PSA recurrences can occur more than 5 years postoperatively. This paper provides powerful evidence that serial DRE or imaging studies are not needed in men following radical retropubic prostatectomy who have an undetectable serum PSA level. The implications of this study for potential decreases in medical costs as well as discomfort and inconvenience for patients are immense.

The indications for anastomotic biopsy for men with detectable serum PSA levels following radical prostatectomy have not been well defined in the literature. Nudell and colleagues[18] from the University of California at San Francisco compared patients receiving postoperative radiotherapy (RT) for a detectable PSA alone following radical prostatectomy with those receiving salvage RT only after both a detectable PSA and a positive anastomotic biopsy. Patients were fol-

lowed for an average of 38 months and were matched with respect to preoperative and pathologic characteristics. Actuarial disease-free survival was similar in both groups. The authors concluded that the result of an anastomotic biopsy did not influence the results of adjuvant RT to the prostatic bed following a PSA recurrence after radical surgery for localized prostate cancer. A negative anastomotic biopsy following an isolated biochemical recurrence after surgery can demonstrate 1 of 3 things: 1) local recurrence present but missed by inadequate biopsy technique or sampling error, 2) lack of local recurrence in the face of distant disease, or 3) a combination of a missed local recurrence as well as the presence of distant disease. In addition, while a positive anastomotic biopsy may represent local disease recurrence, it does not rule out the possibility of synchronous distant metastases. Thus, neither possible result of anastomotic biopsy provides much help in deciding whether to initiate adjuvant RT in the face of a biochemical recurrence after surgery. Furthermore, multiple biopsies may be required before a positive biopsy is obtained, delaying the initiation of salvage therapy and potentially adversely affecting cancer control. This study documents these dilemmas and highlights the lack of clinical utility of anastomotic biopsy.

Mohan and associates[19] reviewed the records of over 2,000 consecutive men presenting with clinically localized prostate cancer and treated over the last decade to determine the influence of neoadjuvant or adjuvant androgen deprivation (AD) therapy on biochemical disease-free survival after either radical prostatectomy or RT. The radical prostatectomy and RT groups in this study each contained just over 1,000 men. AD was used in the initial treatment of 20% of these men. The authors investigated biochemical (PSA) recurrence and controlled for demographic, clinical, and pathologic variables. At a median follow-up of 26 months, the authors demonstrated that the combination of AD therapy and RT provided improved biochemical disease-free survival rates compared with RT alone. They were unable to document a significant effect on biochemical disease-free survival when AD therapy was used in combination with radical prostatectomy. Previous studies investigating the use of adjuvant AD therapy in combination with RT have shown similar improvements in biochemical disease-free survival. This study confirms the results of multiple previous studies documenting a lack of improvement in cancer control, despite statistically significant decreases in surgical margin rates associated with the use of neoadjuvant AD therapy with radical prostatectomy.

Hanks and colleagues[20] investigated whether a survival advantage was conferred by the use of high dose RT compared with low dose RT. This retrospective study compared high and low dose radiation therapy, with the end points being biochemical disease-free survival, freedom from distant metastases, and both overall and cause-specific survival. Over 350 men who received high dose RT (>74 Gy) were compared with 350 men who received low dose RT (<74 Gy). Groups were matched with respect to clinical stage and Gleason score. The group receiving high dose therapy demonstrated a significant improvement in 5-year biochemical freedom from disease compared with those receiving the low dose therapy. Freedom from metastases, cancer-specific, and overall survival were also improved in the high dose group. Multivariate analysis demonstrated that radiation dose was an independent predictor for all end points. This is the first study demonstrating a survival advantage for a specific radiation treatment delivery technique and further documents cancer control outcomes after definitive RT for treatment of men with clinically localized prostate cancer. The authors point out that these high dose treatment algorithms require 3D conformal technology. While not randomized, this study certainly documents the clinical utility of this form of high dose 3D conformal radiation therapy for treatment of patients with clinically localized prostate cancer.

Kattan and associates[21] built on a recently published algorithm[22] for the prediction of disease recurrence following radical prostatectomy. This algorithm provided clinicians and patients with the ability to use pretreatment clinical and pathologic variables to predict the probability of cancer recurrence following radical prostatectomy. The current study presents a multi-institutional validation of this algorithm. The probability of disease recurrence was calculated using the previously published nomogram. A concordance index was used to compare predicted with actual outcomes. The concordance index for the patients in this validation study was somewhat lower than those presented in their original publication (0.61-0.68 vs 0.74). However, the 95% confidence intervals overlapped those reported in the original study and provided evidence that this algorithm can predict accurately the probability of cancer recurrence following radical prostatectomy. This nomogram may ultimately prove to be a valuable tool in helping men with localized prostate cancer—and their physicians—make rational decisions regarding the timing and need for adjuvant therapy. In addition, this type of model may aid the development and evaluation of new therapies for treatment of localized prostate cancer.

The authors of a multi-institutional study[23] documented that biochemical (PSA) failure following radical prostatectomy occurs primarily in patients with positive margins, seminal vesicle invasion, or positive lymph nodes. In this important paper,

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they report the use of a genetic adaptive neural network to predict biochemical (PSA) recurrence. Nearly 300 patients with clinically localized prostate cancer who had undergone systematic prostate biopsy and PSA evaluation prior to prostatectomy formed the study population. The postoperative outcome assessed was presence or absence of biochemical disease recurrence. Menon and associates found that preoperative variables, including serum PSA, biopsy Gleason score, and various pathologic variables obtained from the systematic biopsy material, as well as the findings at pathologic stage, could accurately predict disease recurrence following a radical prostatectomy when used as input variables for a neural network. This network achieved an overall accuracy of 79% on the validation set in this study. This new and exciting technology for analysis of complex multivariable data sets is proving to be useful in diagnosis, clinical decision making, and progression prediction. We will see more information regarding this technology in the near future as it becomes part of our clinical practice. [Dr. Partin, Dr. Potter]

Prostatectomy Technique

The morbidity following radical prostatectomy has been greatly diminished owing to advances in surgical technique, the greater number of surgical procedures being performed for the management of localized prostate cancer, and the increased experience of surgeons performing the procedure. In the hands of surgeons skilled at performing radical prostatectomy, operative mortality is less than 0.5 of 1%, significant technical complications such as rectal and ureteral injuries occur less than 1%, and the incidences of cardiovascular complications including myocardial infarction, cerebrovascular deep venous thrombosis, and pulmonary embolism are less than 2%. The length of hospitalization is typically 1 to 3 days. The overwhelming majority of men gain complete urinary control within 3 to 6 months. The primary morbidity associated with radical prostatectomy remains erectile dysfunction, even when the nerve-sparing procedure is performed properly. Therefore, technologic advances that diminish erectile dysfunction following radical prostatectomy would greatly minimize the complications associated with the procedure.

Klotz and colleagues reported at the AUA meeting a randomized phase III study of intraoperative cavernous nerve stimulation with penile tumescence monitoring (Cavermap™), a surgical aid to improve nerve sparing during radical prostatectomy.[24] The Cavermap is a device that delivers an electrical current to the cavernous nerve with a hand-held nerve stimulator, and tumescence/detumescence is monitored using a sensor placed around the penis. The authors are to be congratulated for performing a randomized trial. A total of 61 men were enrolled in the study. Data at 1 year were available for 53 subjects. Of these 53 men, 45 underwent bilateral nerve sparing, and 8 underwent unilateral nerve sparing. Overall, 68% of the men undergoing bilateral and 27% of the men undergoing unilateral nerve sparing exhibited return of erectile function as measured by the SFIQ (Sexual Function Inventory Questionnaire). Rigiscans™ were performed on all men pre- and postoperatively. The mean minutes with >60% rigidity measured by the Rigiscan at 12 months follow-up was 15.9 versus 2.1 in the Cavermap and conventional nerve-sparing groups, respectively (P=0.02). The erectile potency at 12 months reported by the patients was 71% versus 62% for the Cavermap and conventional nerve-sparing groups, respectively (P>0.05). Interestingly, those men exhibiting a tumescence response at the time of surgery (immediately following the radical prostatectomy) had better return of erectile function measured by Rigiscan. While intraoperative use of the Cavermap appeared to improve Rigiscan results, the impact on return of sexual performance appears to be modest. It is unclear whether this modest advantage justifies the increased operative time and cost associated with the device. Larger studies are required to confirm these preliminary observations. The fact that some efficacy was observed is encouraging. This study provides the rationale for further refinements in the technology and technique. [Dr. Lepor]

PSA and Other Serum Markers

Once again PSA and related serum markers comprised a major theme at the meeting in Dallas. Approximately 5% of the presentations, including 56 on PSA alone, were in the broad category of serum markers, indicating the continual enthusiasm on the part of investigators for this subject.

Gomella and associates[25] continue their investigations to detect circulating prostate cancer cells. They described a quantitative assay that allows accurate assessment of the circulating tumor burden. CellSpotter™ utilizes magnetically labeled cells in a magnetic separator for accurate quantitation. In this novel approach, they showed a stepwise increase in the number of circulating cells between normal controls, 1.0 ± 0.2, versus 4.2 ± 1.0 in men with clinically localized prostate cancer and 81.0 ± 41.9 in patients with established metastatic disease. This approach may obviate many of the problems associated with the reverse transcriptase polymerase chain reaction (RTPCR) assay, which has essentially led to its falling into disrepute, and yet allow clinically useful information to be derived from the quantitation of circulating cancer cells. Of course, large clinical trials showing not only methodologic ability but also clinically important staging and

Table 1
Specificity of Serum Markers in Men With PSA Levels Between 2.5 and 4.0 ng/mL (ROC curve analysis)

Marker	Area under the curve Specificity
F/tPSA	73.9%
PSA-TZ	70.1%
PSAD	60.7%
PSAV	56.3%
PSA	57.7%

ROC, receiver operating characteristic; f/tPSA, free-to-total prostate specific antigen; TZ, transition zone; PSAD, prostate specific antigen density; PSAV, prostate specific antigen volume.

prognostic information will be essential.

Djavan and associates[26] carried out an investigation in which they compared serum PSA, the free-to-total (f/t)PSA ratio, PSA density, and transition zone density along with PSA velocity in men with a total PSA (tPSA) between 2.5 and 4.0 ng/mL. Motivated by the increasing interest in lowering the threshold for biopsy to levels <4.0 ng/mL because of the relatively high prevalence of cancer in men with PSA levels between 2.5 and 4.0 ng/mL, the authors studied 207 men with benign histology and 66 men with prostatic carcinoma. TZV, f/tPSA ratio, PSA transition zone density, PSA and total density, along with PSA velocity all offered significant stratification between those with and without prostatic carcinoma. ROC curve analysis (Table 1) showed that the f/tPSA ratio along with transition zone density were the 2 best predictors of who had carcinoma. As we push the threshold for indication for biopsy lower, problems with specificity will become ever increasingly important. This report suggests 2 derivatives to add in selecting patients for biopsy.

A group of Johns Hopkins investigators[27] examined the utility of total, free, and complexed PSA (cPSA) to identify men with carcinoma with a tPSA <4.0 ng/mL. Eighty-five men were examined, 28% of whom had prostatic carcinoma. At 58% sensitivity, markers showed the following specificities: tPSA, 39%; fPSA, 47%; %fPSA, 53%; cPSA, 43%, %cPSA, 56%—a not unreasonable level of performance, given the relatively low prevalence of carcinoma in this cohort. The authors concluded that approximately half of the unnecessary biopsies could be eliminated utilizing the f/tPSA ratio or cPSA determination and still allow detection of about 60% of those men with carcinoma. Men with low PSA may be the most important population for whom to use either the f/tPSA ratio or cPSA determination. Obviously, to identify this cohort, tPSA will be measured. In this setting, it probably is more appropriate to use cPSA as the second analyte, since this does provide a slightly increased specificity with no diminution in sensitivity.

Another investigation of potential specificity enhancement in men with a tPSA of <4.0 ng/mL was reported by the Seattle group.[28] These investigators measured tPSA and f/tPSA (Hybritech method) along with the cPSA (Bayer Corporation) in 156 men. All men underwent at least 6 systematic sector biopsies, and carcinoma was detected in 21. No significant difference in prostate volume or age in men with and without carcinoma was seen. PSA and cPSA was higher in men with carcinoma. However, f/tPSA did not offer any overall specificity enhancement. Figure 4 demonstrates that cPSA offered the best prediction of stratification at fixed sensitivities. The fact that more than half of negative biopsies could be eliminated and three-quarters of cancers detected if the cPSA were utilized suggests a very important role for this new marker. The significance of the cancers detected is supported by the observation that two-thirds of the men with malignancy had Gleason scores ≥6, and cancer was detected in more than 1 core in all but 8.

The group from Hamburg, Germany,[29] asked the question: Is it important to biopsy men with a PSA <4.0 ng/mL? They studied 202 men undergoing radical prostatectomy and categorized them into PSA ranges (2-4, >4-6, >6-8, >8-10, and >10-12 ng/mL). They measured total cancer volume (cv), cancer volume of Gleason grade 4 (cvGl4), pathologic stage (ps), rate of positive margin (pm), and prostate volume (pv) within each of the ranges. There were no significant differences in cv and cvGl4 between the first 3 PSA groups (2-4, >4-6, >6-8). The authors concluded that because there is no pathologic difference between those men with a PSA less than versus greater than 4.0 ng/mL, there is no reason to use a threshold for indication for biopsy of <4.0 ng/mL. Rather, men should be followed with serial examinations and biopsy performed only when PSA exceeds the 4.0 ng/mL threshold.

Forster and associates[30] from Basel, Switzerland, evaluated the effect of storage on the fPSA and tPSA levels in men undergoing systematic sector biopsy. Carcinoma was found in 25%. They performed f/tPSA ratio measurements immediately and on sera processed and stored at -20ºC for 15 months. They observed a slight reduction in the tPSA level from a mean of 6.6 to 6.3 ng/mL. This did not achieve statistical significance. In contrast, both the fPSA and the f/tPSA ratio decreased significantly with storage. Applying cutoffs from studies utilizing frozen sera to those generated from immediately processed patient material may result in significantly misleading results.

The stability of the fPSA analyte was also the subject of an investigation by Kranse and associates.[31] Sera samples from 356 patients were analyzed initially and 3 years later. The ratio for second and first samples of

PSA was 0.972. For the fPSA, the mean ratio was 0.94. Other parameters, such as times between thawing and processing the sample, could not be controlled for. This report does confirm previous suggestions that the free form of PSA is less stable than PSA complexed with protease inhibitors.

Given the problems observed in the above paper, which confirmed other studies, Ferreri and colleagues[32] from Seattle carried out an investigation on the effect of long-term storage of serum on the complexed form of PSA. Utilizing the Immuno 1™ (Bayer Corporation) investigational method for measuring cPSA, these authors examined sera from 29 patients; sera were analyzed initially and 18 months later. The sera had been stored at -80°C. Different lots of reagents, technicians, and Immuno 1 instruments were utilized in this study between the first and repeat cPSA determination. Figure 5 demonstrates the substantial equivalence between the initial cPSA level and that observed 18 months later. These data demonstrate that cPSA is extremely stable, which should allow extrapolation of results obtained from archived sera to fresh sera in the clinical arena.

Shariat and colleagues[33] reported on a single investigator's comparison of serum PSA, PSA density, and transition zone density in 230 men undergoing biopsy. Predictors of carcinoma included age, prostate volume, TZV, total gland density, transition zone density, and peripheral zone density. They have confirmed other investigators' findings that larger glands have a lower rate of prostatic carcinoma detection (26.9% for men with glands smaller than 30 mL versus 11.8 for those with 60 mL or larger prostates). Total gland density performed better than PSA, and no additional enhancement with transition zone density was observed. The f/tPSA was increasingly valuable in the larger prostates. In contrast, gland density was less informative in larger prostates. In glands <30 mL, PSA performs as well as any other parameter. In midsize glands, density calculations perform better than PSA alone. In prostates ≥60 mL, neither PSA nor total gland density performed as well as the f/tPSA ratio.

The lack of specificity of our diagnostic tests for prostatic carcinoma results in approximately 2 of every 3 men who undergo biopsy having

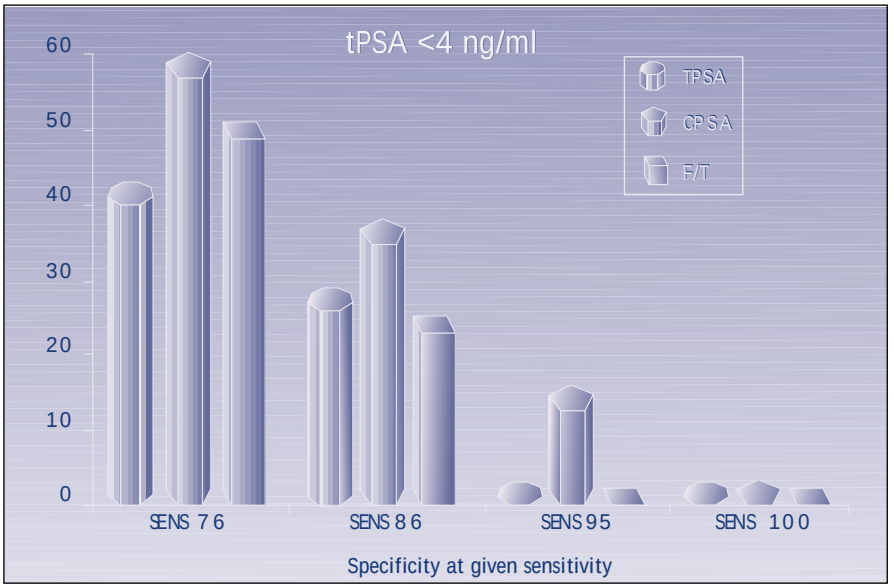

Figure 4. In a study of 156 men, cPSA was the best predictor of stratification of fixed sensitivities.

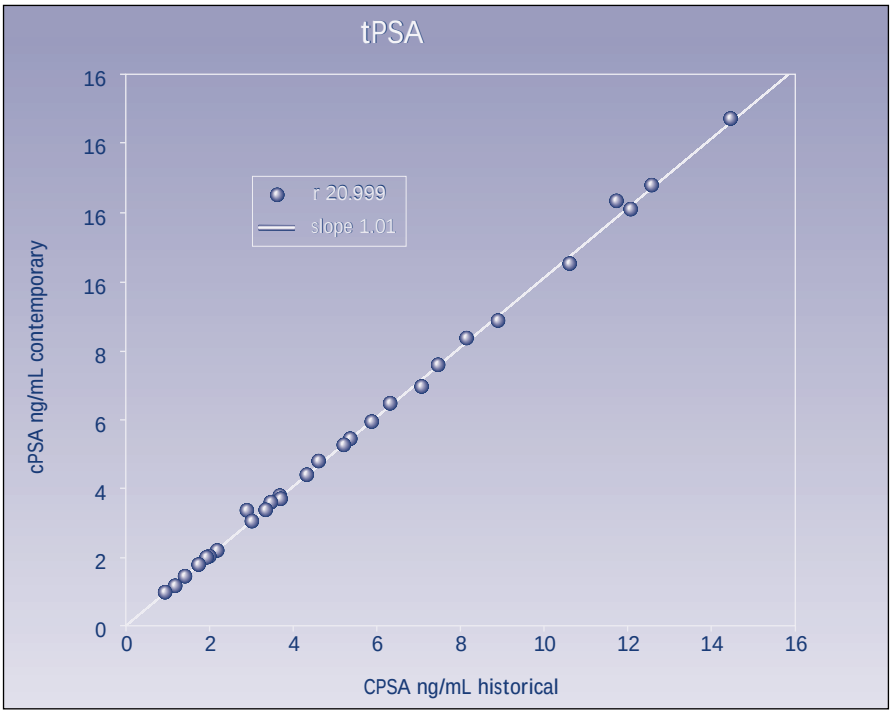

Figure 5. Measurements of a cPSA initially and of stored sera 18 months later indicate substantial equivalence and stability.

Table 2
Median Values and *P* -Values According to Mann-Whitney U Test for A. All Biopsied Men and B. Men With PSA-T 3-10 ng/mL

	A Benign n = 407	Cancer n = 197	*P* value	B Benign n = 391	Cancer n = 150	*P* value
PSA-T (ng/mL)	4.1	5.4	<0.0001	4.0	4.6	0.0003
PSA-F/PSA-T (%)	18.4	12.6	<0.0001	18.5	14.0	<0.0001
hK2 (ng/mL)	0.058	0.076	<0.0001	0.056	0.068	0.0008
hK2 x PSA-T/PSA-F	0.31	0.59	<0.0001	0.31	0.50	<0.0001

PSA-T, prostate specific antigen-total; PSA-F, prostate specific antigen-free; hK2, human kallikrein type 2.

Table 3
Patients With Positive TRUS Biopsies (Median ± SE)

	AA n = 82	Other n = 191	AA vs other
Age	68.6 ± 0.8	66.8 ± 0.5	*P*=0.054
PSA	17.6 ± 3.3	9.5 ± 1.6	*P*=0.001
PSAD	0.46 ± 0.1	0.25 ± 0.05	*P*=0.001
TRUS volume	36.8 ± 2.7	37.8 ± 1.7	*P*=0.82

SE, standard error; AA, African American; PSA, prostate specific antigen; PSAD, prostate specific antigen density; TRUS, transrectal ultrasound.

benign findings. Stenman and associates[34] carried out a logistic regression analysis in which input parameters included age, fPSA, tPSA, f/tPSA ratio, DRE results, TRUS findings, and family history. Two hundred and twelve men who were part of the European Randomised Prostate Cancer Screening study were evaluated. Carcinoma was found in 53 (25%). The logistic regression model resulted in 87% sensitivity and 41% specificity. The authors concluded that the logistic model was more accurate in a biopsy population than multistep algorithms. They demonstrated, for example, that the cancer probability was similar if a man has a tPSA of 4.0 ng/mL, an average f/tPSA range, and a normal DRE as compared with another man with a tPSA of 30 ng/mL and a f/tPSA ratio of 40%. Obviously, as increasing variables are considered and our databases become more extensive, refined cancer risk assessment models will allow more precise counseling of patients and more appropriate selection for biopsy.

Considerable interest followed the early suggestion that insulin-like growth factor (IGF) was shown to be a potent mitogen for prostate cancer cells. Additionally, some authors have showed elevation of serum IGF in men with prostatic carcinoma. Bradley and associates[35] measured IGF in 171 men being evaluated for prostatic disease. One hundred and seven had malignancy. They observed no significant difference in the IGF levels in men with or without malignancy. In contrast, Seitz[36] demonstrated higher IGF levels in 60 men with prostate cancer as compared with 98 without. Furthermore, they showed that the ratio of IGF-1/PSA and IGF density was able to enhance the discriminate ability to diagnose cancer. These 2 conflicting reports warrant further investigation of this potentially useful additional marker.

A group of investigators from Finland[37] studied 615 men with a PSA >4.0 ng/mL. These authors demonstrated that there was no difference in IGF or IGF-binding protein in men with or without prostatic carcinoma. In another report on IGF, Slawin and associates[38] evaluated 122 men with clinically localized prostate cancer undergoing radical prostatectomy. They measured serum IGF level and observed no correlation with preoperative PSA, final Gleason grade, pathologic stage, or risk of PSA progression with a median follow-up of 33.6 months. PSA did correlate with the final Gleason score but not with pathologic stage.

Human kallikrein type 2 (hK2) is another neutral serine protease that has considerable sequence homology to PSA. In a multicenter investigation, Boeken Kruger and associates[39] evaluated 171 men with clinically localized prostate cancer scheduled for radical prostatectomy and 88 men without evidence of prostate cancer on either biopsy or transurethral prostatic resection (TURP). They measured hK2 and tPSA. The authors observed that, particularly in the tPSA range between 4.0 to 10.0 mg/mL, adding hK2 resulted in significant enhancement in a ROC curve analysis of stratification of those men with or without prostatic carcinoma. Obviously these data are encouraging. However, they must be replicated in a prospective biopsy population.

Catalona and associates[40] carried out an investigation combining the %fPSA and hK2 levels in men with a low PSA between 2.0 and 10 ng/mL. Twenty-one percent had carcinoma,

56 of the 368 with a PSA between 2.0 and 4.0 ng/mL. These authors demonstrated that when hK2 was combined with f/tPSA, it generated significant enhanced sensitivity at high specificities in the 2.0 to 4.0 ng/mL level where this is so important. Larger multicenter trials will be necessary before the combination of these 2 molecular forms of PSA can be utilized for widespread clinical utility.

In another study of hK2, Becker and associates[41] evaluated men participating in the Göteborg [Sweden] Screening Study. They studied 104 men undergoing biopsy and 199 who did not. The latter group were men with a tPSA of <3.0 ng/mL. The authors observed that hK2 concentrations were significantly higher in men in whom cancer was diagnosed as compared with those with benign findings. Table 2 shows the significant findings. At 95% sensitivity, the tPSA provided a specificity of 13%; f/tPSA ratio, 17%; and hK2 × PSA−T/PSAf, 18% specificity. Again, further work is necessary before clinical utility of this marker can be recommended.

The impact of racial differences on diagnostic testing for prostatic carcinoma continues to be an area of interest. The Dallas group[42] evaluated a number of parameters in African Americans and Caucasian men presenting for ultrasound-guided prostate biopsy. Six hundred and ninety four men were evaluated at the North Texas Veteran's Health Care system, including 176 African Americans. Two hundred and seventy three men were shown to have carcinoma (39.3%), including 82 of the African Americans (46.6%). They found the cancer detection rate was higher in African Americans (*P*=0.028). Age was a statistically significant predictor of carcinoma in both racial groups. There was no difference in PSA, ultrasound findings, or PSA density between races in men with benign histology on biopsy. In men

Table 4
Serum Assay Results for Various Molecular Forms of PSA (n=375)

	Average ± SD			
Variable (Total PSA range = 1.7 - 25.9 ng/mL)	BPH (n=185)	Cancer (n=190)	*P*-Value	ROC AUC
Patient age (years)	67.9 ± 7.0	69.0± 8.9	0.1901	55.1%
Bayer total PSA (ng/mL)	7.77 ± 4.47	8.55 ± 4.88	0.1066	54.5%
Bayer complexed PSA (ng/mL)	6.45 ± 4.01	7.54 ± 4.60	0.0153	57.1%
Bayer (calculated) free PSA (ng/mL)	1.31 ± 0.80	1.01 ± 0.67	0.0001	63.0%
Abbott (measured) free PSA (ng/mL)	1.54 ± 1.04	1.15 ± 0.74	<0.0001	62.7%
Abbott free/Bayer total PSA ratio (%)	21.5 ± 11.0	15.5 ± 10.8	<0.0001	69.9%
Bayer free/total PSA ratio (%)	18.6 ± 8.3	13.6 ± 8.0	<0.0001	69.4%
Bayer complex/total PSA ratio (%)	81.4 ± 8.3	86.4 ± 8.0	<0.0001	69.4%

SD, standard deviation; PSA, prostate specific antigen; BPH, benign prostatic hyperplasia; ROC, receiver operating characteristic; AUC, area under the curve.

Table 5
Sensitivity, Specificity and Area Under the ROC Curves (global series)

Assay	Cutoff	Sensitivity (%)	Specificity (%)	Area under curve
PSA-T (T)	>0.66	100	4.8	0.782
	>2.6	95.3	27.3	
	>4.0	90.2	40.9	
	>4.7	85.1	48.8	
PSA ACT (C)	>0.54	100	7.5	0.829
	>2.0	95.3	32.5	
	>3.4	90.2	52.5	
	>4.0	85.1	59.6	
C/T (%)	>49	100	9.0	0.888
	>65	95.3	36.0	
	>72	90.0	66.0	
	>75	85.9	76.9	

ROC, receiver operating characteristic; PSA-T, prostate specific antigen-total; PSA ACT, prostate specific antigen, α_1-antichymotrypsin

Table 6
Sensitivity and Specificity Comparing f/tPSA With cPSA

	Sensitivity				Specificity			
TPSA	n	TPSA[1]	cPSA[2]	%fPSA[3]	n	TPSA[2]	cPSA[3]	%fPSA[3]
ALL	272	90	85	86	385	28	41	36
4-10 ng/mL	202	100	93	96	237	0	21	13
4-6 ng/mL	74	100	81	100	127	0	37	13

[1]Cutoff, 4.0 ng/mL; [2]cutoff, 3.75 ng/mL; [3]cutoff, 25%.
f/tPSA, free/total prostate specific antigen; cPSA, complexed prostate specific antigen; TPSA, total prostate specific antigen. Adapted with permission from *J Urol*.[46]

Table 7
Cancer Probabilities

% Free PSA range	Prostate cancer probability	(95% confidence interval)
≥10%	70%	(60% - 80%)
>10-11%	58%	(49% - 67%)
>11-15%	46%	(39% - 53%)
>15-20%	34%	(28% - 40%)
>20-24%	23%	(18% - 30%)
>24-26%	15%	(11% - 22%)
>26%	10%	(6% - 16%)

PSA, prostate specific antigen.

Table 8
Comparing F/TPSA Assays

ASSAY	Sensitivity (%)	Specificity (%) total PSA	Specificity (%) F/T PSA	Cut-point total PSA (ng/mL)	Cut-point F/T PSA (%)
ACS:180	100	0	0	0.02	90
	95	10	17	1.7	25
	90	25	54	3.3	15
Enzymun	100	0	0	0.02	100
	95	5	7	1.1	43
	90	24	32	3.0	23
Tandem-R	100	1	1	0.4	52
	95	7	22	2.1	25
	90	17	31	3.4	21

F/TPSA, free/total prostate specific antigen; ACS:180, Chiron Diagnostics; Enzymun, Enzymun Boehringer Mannheim; Tandem-R, Hybritech. Reproduced with permission from *J Urol*.[49]

with malignancy, African Americans had higher PSA and PSA density compared with Caucasian men (see Table 3). The authors concluded by suggesting different biologic behavior regarding production, release, leakage, or metabolism of PSA between races. Nothing in this paper should be construed to indicate that different thresholds of PSA level should be utilized in African Americans to select men for biopsy as compared with Caucasians.

With reliable methods now available to measure the antichymotrypsin (ACT)-complexed form of PSA, Veltri and associates[43] contrasted this assay with the f/tPSA ratio. They evaluated 375 men; 190 were shown to have malignancy. They evaluated the total and cPSA assays (Bayer) with the fPSA (Abbott). They observed that both the f/tPSA either measured directly or by calculating the free by subtracting cPSA from tPSA provided significant enhancement based on ROC analysis. Table 4 shows the major findings.

Sarmiento and associates[44] carried out an investigation of α_1-ACT cPSA/tPSA ratio. They studied 710 patients, 255 of whom had carcinoma, and observed that tPSA, PSA-ACT complex, and the ratio of complexed to total PSA all were significantly higher in men with carcinoma. In addition, the prostate volume was significantly smaller in those with malignancy. Table 5 shows the significant findings. At the level of 95.3% sensitivity, tPSA provided specificity of 27.3%, ACT-complex, 32.5%, and a ratio of complexed to total specificity of 36%.

The Stanford group[45] compared cPSA and f/tPSA in men undergoing biopsy. They evaluated 170 patients and, to their credit, elected to perform repeat biopsy in the 90 men with negative biopsy results to confirm the negative status. The 80 men with prostate carcinoma were selected such that at least all had 5 mm of

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Table 9
Cancer Probability Based on Age, PSA Level, and DRE Results

PSA ng/mL	40-50 yrs.		51-60 yrs.		61-70 yrs.		71-80 yrs.	
	DRE	DRE+	DRE	DRE+	DRE	DRE+	DRE	DRE+
0.0-2.5	9%	37%	12%	39%	15%	42%	20%	44%
2-6-4.0	9%	41%	12%	42%	16%	44%	20%	47%
4.1-6.0	10%	41%	14%	44%	17%	47%	22%	48%
6.1-10.0	11%	—	15%	48%	19%	50%	25%	52%
10.1-20.0	13%	55%	19%	54%	25%	58%	31%	60%
>20.0	22%	82%	45%	74%	43%	81%	59%	84%

PSA, prostate specific antigen; DRE, digital rectal examination. Reproduced with permission from *J Urol*.[53]

cancer on their needle biopsies. Multiple PSA assays were utilized. Of note, the tPSA was indistinguishable (10.9 ng/mL) between those with or without carcinoma. The authors demonstrated that the ratio of cPSA to tPSA or fPSA to tPSA all had significantly increased performance by area under the curve analysis compared with cPSA alone.

In contrast, Brawer and associates,[46] reporting on a multicenter investigation, demonstrated substantial equivalence in the performance of the f/tPSA by utilizing the Hybritech method as compared with the cPSA using the Bayer method. Table 6 shows the significant results.

A number of differences between the multicenter trial and the Stanford experience exist. In addition to larger numbers and the absence of repeat biopsies in the benign in the former and minimum length of cancer in the positive biopsies in the latter series, there was a significantly different level of PSA in those men with and without carcinoma in the multicenter trial. This suggests that the major differences between these 2 investigations stems from patient selection and underscores the need for broader-based trials.

In a screening population, the cPSA appears to perform greater stratification in tPSAs that are lower, such as between 4.0 and 6.0 ng/mL, and the f/tPSA ratio provides better stratifying information in the higher tPSA ratios—say, 6.0 to 8.0 ng/mL. Of note is that in a screening population, a far greater number of men have a PSA between 4.0 and 6.0 ng/mL than between 6.0 and 8.0 ng/mL.

A report by Catalona and associates of a multicenter trial demonstrating the utility of the f/tPSA ratio in men with a PSA between 4.0 and 10.0 ng/mL utilized the Hybritech method.[47] The report by Chan and associates[48] confirmed these findings utilizing the dual monoclonal assay method (Abbott AXSYM). Just as in the original study, they selected men with a negative DRE and a tPSA between 4.0 and 10.0 ng/mL. Three hundred and seventeen men were evaluated. One hundred and seven men had carcinoma. Table 7 shows the significant results. Of note, utilizing virtually identical cutoffs to achieve 95% sensitivity, such as was found in the report by Catalona, the study demonstrates that substantially equivalent specificities were realized. It is imperative that all manufacturers provide data similar to this so that clinicians can apply cutoffs generated with the assay they are using and not be forced to extrapolate from the literature cutoffs that may be inappropriate.

The absence of a national standard for tPSA or fPSA and considerable variability between different manufacturers results in a significant clinical dilemma. One cannot extrapolate from published literature if different assays are utilized. Roth and associates[49] addressed this subject by comparing 3 different manufacturers' fPSAs and their respective tPSAs. Two hundred and forty men were evaluated, 79 of whom had carcinoma. Table 8 shows the significant findings. Of note, this work was performed on fresh serum. Thus, this degradation of the free PSA as reported above was unlikely a cause of performance problems. As shown, different cutoffs must be utilized to afford the same level of sensitivity between manufacturers. Clinicians must be aware of which assays for both the fPSA and tPSA are being utilized and, ideally, performance characteristics derived from similar patient populations undergoing biopsy should be supplied by the manufacturer.

Research for additional molecular forms of PSA continues. Mikolajczyk and associates[50] reported on a specific "B-PSA" - type of fPSA that occurs in higher concentration in BPH-associated transition zone as compared with benign or malignant peripheral zone tissue. Transition zone BPH was found to contain increased levels of a clip form of PSA, which they have called B-PSA. The increased serum fPSA found in men with BPH may be due to an increase in this specific form of PSA. Ultimately, this may provide enhanced differentiation of those men with moderately elevated PSAs with and without carcinoma.

Nomoto and colleagues[51] reported on the isolation of a gene encoding a novel serine protease named hippostasin utilizing degenerated polymerase chain reaction (PCR) technique. This new protein has 40% sequence homology to PSA. Utilizing immunohistochemistry and in situ-2 hybridization, these authors demon-

strated expression of this marker and the gene encoding it in prostatic epithelial cells. Obviously the next step is the development of an immunoassay. This protein may represent a new target for a novel marker in prostate carcinoma.

Another novel potential marker for prostate carcinoma is the so-called human carcinoma antigen (HCA). Taylor and associates[52] evaluated this pan-tumor marker that is expressed in human prostate cancer but not in benign prostatic tissue. In an evaluation of 439 men undergoing ultrasound-guided prostate biopsy because of a serum PSA >4.0 ng/mL and/or abnormal DRE, they showed that HCA outperformed serum PSA. HCA had a specificity of 92.2% compared with PSA's 51.6%. In terms of sensitivity, HCA was 96.4% while PSA was 81.5%. Abnormal HCA was defined as a level >300 ng/dL; abnormal PSA was defined as >4.0 ng/mL. These results were impressive and, if confirmed, may represent a novel marker of great utility.

Ultimately, risk assessment for malignancy is what should drive the decision for biopsy rather than a simple cut point. Subong and associates,[53] utilizing the extensive database associated with the Tyrol Screening Project from Austria, performed logistic regression analysis on 2054 men undergoing biopsy. The input parameters included patient age, serum PSA level, and DRE findings. Table 9 shows the major findings. Similar cancer probability tables should be provided on representative populations. Perhaps this will provide a useful tool to counsel a patient on the likelihood of carcinoma and thus allow him to make a decision in conjunction with the urologist as to the potential benefits of a biopsy.

These reports highlight some of the major research activities in serum markers. Undoubtedly, several of these findings will provide benefit to our patients. [Dr. Brawer] □

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