



PCRI Insights

Patient & Physician in Co-Partnership

New Developments in Prostate Cancer Treatment

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The PROSTATE CANCER CONFERENCE

September 6-7, 2008

Los Angeles, CA

Sheraton Gateway Hotel Los Angeles



More to See and Do at the PCRI Conference

The 2008 Annual Prostate Cancer Conference gives attendees the unique chance to hear from top doctors and professionals and learn about cutting-edge treatment options. PCRI understands that the need for patients and caregivers to have access to this important information, while at the same time, providing time to relax and connect with other patients and families facing this disease. As part of the conference schedule, we hope you'll join us for our Friday night excursion to the famous Hollywood Bowl, the Saturday night Gala Dinner and the sunset cruise on Sunday night. (Continued on page 34.)

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This Part III extends Dr. Strum's thesis to the diagnosis of PC. He covers five areas in depth: (1) the "normal" range of PSA between 0.0-4.0 ng/ml, (2) recommendations not to check PC, (3) the use of free- to total-PSA percentage, (4) the use of nomograms and neural nets in PC diagnosis, and (5) the use of PSA velocity (PSAV), PSA Doubling time (PSADT), and PSA density (PSAD) tools that "are not used nearly as often as they should be."

14 The European Association of Urology (EAU) Conference. *By Douglas Chinn*

Dr. Chinn attended the EAU Conference in Milan, along with 14,000 participants and over 9000 registered attendees from 84 countries. Of the papers and presentations that particularly interested him, he reports on Real-time Elastography Targeted Biopsy, Contrast-Enhanced Color Doppler, 18F-Fluorocholine and 11c-Choline PET Scan Tracers, Combindex MRI, and Pelvic Lymph node dissection. He also compares the EAU Conference with this year's AUA conference.

22 New Technology Observed at 2008 AUA Conference. *By Jim O'Hara*

Jim O'Hara offers additional insights into the AUA Conference. He reports on the presentations: GPS for the Body, 4D Image Guidance and Navigation for Prostate Biopsy, the Prostate Px Commercial Test to Predict PC Progression and Recurrence at the Time of Diagnosis, 3D Imaging and Targeted Biopsy, and Circulating Tumor Cells as a New Marker for Monitoring PC.

26 Pomegranates and Prostate Health: A Research Report. *By Mark Dreher*

Dr. Dreher reports in depth on a research program that his company, POM Wonderful, LLC, has been conducting and sponsoring. Included have been clinical studies on the positive impact of pomegranate juice products on prostate cancer, bioavailability/pharmacokinetics, antioxidant potency, and drug interaction. Results have been quite positive, and POM is currently sponsoring several clinical trials to further confirm this positive relationship between POM products and reduction of PC risk.

WHAT WE SHOULD HAVE LEARNED ABOUT PROSTATE CANCER (PC) IN THE LAST 10 YEARS, PART 3

Stephen B. Strum, MD, FACP

Overview

In Parts I and II of this series, I presented an in-depth discussion of key issues relating to the chemoprevention of PC, and I discussed in depth the results of the PCPT (Prostate Cancer Prevention Trial) published in 2003, as well as preliminary results of the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) Trial from 2004. I related my surprise and disappointment that the highly significant findings of these trials had not been translated into the every-day care of men at risk for PC. Coincidentally, beginning shortly after publication of Part II, a number of peer-reviewed articles and news briefs have been published attesting to the value of finasteride (Proscar) in the prevention of PC. These articles provided evidence-based medicine to dispel prior findings that using finasteride in the chemoprevention of PC leads to the development of high-grade PC.¹⁻⁵

Will these articles finally spark the use of finasteride in academic and community circles? This remains to be seen. What is clear to me, however, is that if we are to advance in our understanding of the prevention, diagnosis, staging and treatment of PC, we should not tolerate a lag time averaging ten years or more between presentation of key advances and their implementation. Over the 45 years I have been involved in cancer research and treatment, this lapse has been the rule, and rarely the exception. The only force with the potential to change the lugubrious pace in medical advances is that coming from the PC patient community, as we should have learned from the AIDS movement in the USA. Can we utilize those advances relating to the diagnosis and staging of PC — two of the foundation stones relating to the concept of status begets strategy? This is the topic of discussion in this Part III, and in future installments in this series.

Diagnosis of PC

In my opinion, and without any question of doubt, the discovery and use of PSA has been the most important occurrence that has changed our understanding of this disease. In the realm of diagnostic importance, PSA still rules supreme, but there are some relatively “new” kids on the block, such as PCA3 and EPCA, which I will discuss later. The serum PSA and its derivatives such as Free-to-Total PSA ratio, PSAV (PSA velocity), PSA slope, PSA doubling time (PSADT), and PSA density (PSAD), provide significant insights into a man’s status where a diagnosis of PC is the main concern. However, in this area and closely related ones, there are controversial issues that merit discussion of whether or not a man has PC. These are:

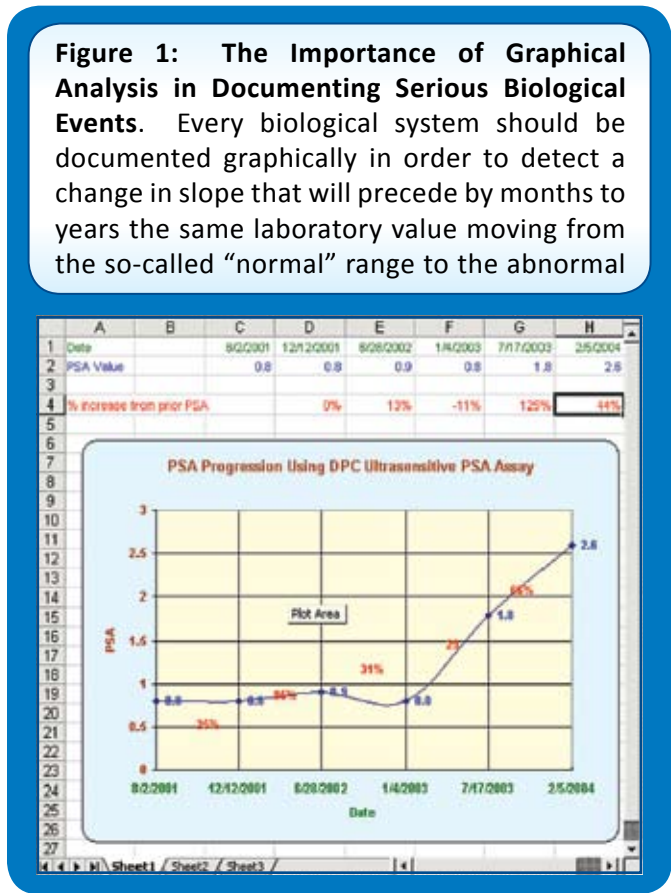
1. The “normal range” of PSA between 0.0 – 4.0 ng/ml
2. Recommendations not to check PSA
3. The use of free- to total-PSA percentage
4. The use of nomograms and neural nets in PC diagnosis
5. The use of PSAV, PSADT, and PSAD

1.0 The Normal Range of PSA Between 0.0 – 4.0 ng/ml

My contention is that there is no normal range of PSA. Seeing a patient present with a delayed diagnosis of PC because the internist, GP, FP or other clinician waited until the PSA was greater than 4.0 is a sad event. This is even more the case with aggressive high-grade PC where PSA production by the tumor cell population is decreased.⁶ The take-home-lesson for PSA is whether the PSA slope is flat, rising, or decreasing in regard both to the issue of the diagnosis of PC, and to virtually all settings relating to PC status.

It is true that a man with repeated PSA values of 1.0 will have a healthy prostate gland 99% of the time. However, a solitary value in that range does not tell us

about what biological events are in progress within the gland; we can only glean that information by knowing the PSA values over time in order to establish status. This need to incorporate the context of time is not only true of PSA in determining whether PC is present, but also for just about all biological – social – human-related events ranging from CO₂ emissions in the atmosphere to how well or badly your stock is doing. Here is where the value of the chart, flow sheet or graph becomes paramount. **This graphical approach is the most obvious means to alert the patient-partner-physician team to the presence of a problem: seeing an unmistakable serial increase in the slope of the PSA, or any other marker shown to be of importance in PC.** Figure 1 depicts this obvious cause for alarm.



Given today’s computer technology, there is no reason that we cannot routinely portray biological values graphically, or at least as a slope value. What we have done is to sacrifice the patient’s chances of an early diagnosis and cure of their illness in exchange for either being too lazy or forgetting to utilize this important tool in our arsenal. **All laboratory reports should be presented with slope findings.** The most painful reminder of the cost of not doing this occurred when I reviewed the records of one of

my former employees who asked for help after her mother was diagnosed with cancer of the stomach. A review of her medical records preceding this diagnosis by years showed (1) a serial fall in the mean cell volume (MCV) of her red blood cells (which reflected the development of iron deficiency) and (2) a serial fall in hematocrit from high-normal to normal, to low-normal, and then to abnormal. These findings, if made obvious to the practitioner, would have beckoned for a diagnostic workup that hopefully would have led to an upper endoscopy that would have indicated gastric cancer – before the disease had spread to the lymph nodes and liver!

In the context of a man with a one-in-six lifetime risk of PC, the take-home-lesson is to obtain a baseline PSA when the man reaches age 40, or age 35 if he has a family history of PC or breast cancer, and to recheck the PSA at reasonable intervals (yearly initially) until a PSA slope or trend is established. If the slope is found to be flat, then continue to sample the PSA at appropriate intervals throughout all of that man’s history. Table 1 below shows my PSA values that have been taken over the course of almost 20 years. *(Continues on page 4.)*

Table 1: PSA Values of Stephen Strum from 1989 to 2008.

Date	PSA
12/11/89	1.2
10/18/91	0.9
5/27/92	1.0
1/31/97	0.8
2/16/98	1.2
7/8/98	0.8
8/5/99	0.71
9/26/00	0.57
8/31/01	0.66
5/28/02	0.89
5/13/04	0.63
2/8/05	0.48
9/7/06	0.90
11/17/06	0.60
10/2/07	0.80
4/28/08	0.93

The values show a general consistency despite the fact that they involve the development of new testing approaches (assays) for PSA such as Yang, Tosoh, and DPC. The potential trend of the last three values (0.60, 0.80, 0.93) mandate the need for a repeat test in the very near future.

These values were not all obtained using the same PSA assay due to the ongoing improvement in assays over the last 20 years. I strongly recommend that (1) you use the same assay, (2) obtain the PSA either in the morning or in the afternoon, (3) restrain from any activity involving ejaculation for 48 hours prior to testing, and (4) not be involved in any examination of the prostate or any athletic activity exerting pressure on the prostate area, e.g. bicycle riding. Although my last three PSA values (obtained between 2006 and 2008) are normal, I do need a repeat value(s) in light of the possible upward slope that may be starting. I concur with the saying that you teach what you need to learn.

2.0 Recommendations Not To Check PSA

I have been shocked to see articles advising men NOT to have PSA testing, stating that this will lead to a treatment such as RP (radical prostatectomy), RT (radiation therapy), Cryosurgery, or HIFU (High Intensity Focused Ultrasound) that could harm the patient and impair his quality of life (QOL). This may be a reality that relates to any kind of human interaction insofar as the quality of a service to be delivered. But it is ridiculous to confuse cause and effect insofar as the value of an early diagnosis of PC.

An early diagnosis of PC, at any age, is a meaningful milestone in the potential welfare of the patient because prostate health is too intimately associated with bone integrity, vascular integrity, lipid abnormalities, the status of carbohydrates, fatty acids and vitamin D, neurologic and male sexuality, and urinary flow issues. In other words, a diagnosis of PC serves as a signal that although not every man with a PC diagnosis needs to be treated, all certainly should be evaluated for co-existing illnesses – illnesses that if unrecognized and untreated may lead to a further decline in health and possibly to death. The fact that more men die with PC than from PC is a testimony to the validity of this statement. Read through the first six Physician's Notes in *The Primer on Prostate Cancer* by Strum and Pogliano and especially focus on

Note 6: "Good comprehensive PC management often leads to the marked overall health of the patient." If 95% of men newly diagnosed with PC have osteopenia or osteoporosis,⁷ and if such loss in bone density has been shown in hundreds of peer-reviewed articles to be associated with cardiovascular disease, renal disease and neurologic disease,⁸⁻¹⁵ then we can perform a huge service to the man with PC by at least focusing our attention on such issues – even if it is determined that no invasive therapy is indicated for the treatment of the PC--the illness that brought the patient to the physician.

Moreover, our decision on whether or not to treat an individual patient with PC should be based on the context of that patient. It should take into account factors such as age, mental status, co-existing illnesses, healthcare costs and access to skilled physicians who may be the principals involved in an invasive procedure. For this reason, I have repeatedly stated that the major ingredients in the successful management of a man with PC are:

1. Selection of the Patient.
2. Choice of a Therapy Appropriate for that Patient.
3. Selection of an Artist.
4. Supportive Care of the Patient Throughout the Entire Life of the Patient.

3.0 The Use of Free-to-Total PSA Ratio

The PSA derivative called Free-PSA is actually a percentage of the ratio of Free-PSA to Total-PSA. The Total-PSA is made up of the Free-PSA in addition to bound or complexed PSA. It is complexed because it is attached to a protein called alpha chymotrypsin (ACT). Therefore, the Free-PSA Percentage = Free-PSA divided by (Free-PSA + Complexed-PSA) with the result multiplied by 100. Values over 25% are most consistent with a benign process, while those less than 15% are worrisome for a diagnosis of PC. Those values in between are in a gray zone.

All the biologic inputs that present circumstantial evidence that PC is likely or is not likely should be used as part of the medical detective work involved in the diagnosis of PC. I have found the Free-PSA percentage to be of great value in the diagnostic

dilemma of “does this man have prostate cancer?” One potential exception to this is if the patient has significant prostatitis; in this case, the free PSA percentage may be quite low, even less than 10%.¹⁶⁻²⁰ However, the PSA slope is entirely different in the context of prostatitis versus PC. Figure 2 shows the typical up and down pattern of prostatitis. There is no trend line that shows serial progression in PSA that is characteristic of PC.

It is disturbing that although there are plentiful papers defining the value of the Free-PSA percentage to help in ruling in or ruling out a diagnosis of PC, I find that this test is often not ordered in many patients, especially in those with low but serial increasing PSA levels.²¹⁻²³ Catalona et al showed the value of the Free-PSA percentage in the PSA range of 2.6 to 4.0 and a normal DRE, but for no obvious reason, this test is usually forgotten in this context. In this important study, all cancers detected were clinically localized, and 81% that were surgically staged by RP were pathologically organ confined.²⁴ In another study by Catalona et al involving men with total PSA levels of 4.0-10.0 and a normal DRE with a gland volume less than 40 cm³, the use of a Free-to-Total percentage threshold of 14% or less would have eliminated 79% of unnecessary biopsies.²⁵

Even less utilized is the use of the Free-PSA percentage over time. In longitudinal evaluations of Total- and Free-PSA (using frozen sera) among men who were diagnosed with PC in the pre-PSA era, Pearson et al demonstrated that Total-PSA increases while the Free-PSA percentage decreases over the decade prior to the diagnosis of PC. If a Free-PSA percentage cut-off of $\leq 10\%$ is used as a marker for PC, the longest lead time of 9.7 years was obtained. Unfortunately, at this cut-off there were too many false positive predictions of PC among the control cases, especially for Total-PSA values of < 2.0 ng/ml. This resulted in a low specificity of 59%. But, with a Free-PSA percentage cut-off of $\leq 12\%$, when Total-PSA levels were 4.0 or higher, the specificity for predicting a correct diagnosis of PC was 94%.²⁶ The average curves for Free- to Total-PSA in control and PC patients over a 14-year span are shown in Figure 3.

Rarely do I see physicians monitoring this PSA derivative in undiagnosed patients who are suspected of having PC. Thus, at least part of the PC diagnostic mindset, in my opinion, should be one of seeing

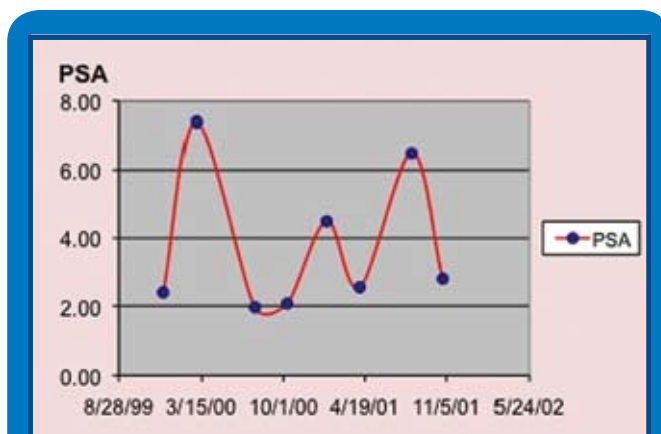


Figure 2: PSA Fluctuations in Prostatitis. This is a typical finding in prostatitis with no clear-cut trend line that one sees in PC. The PSA peaks and valleys may or may not correlate with the patient’s symptoms reflecting the variable clinical manifestations seen with prostatitis.

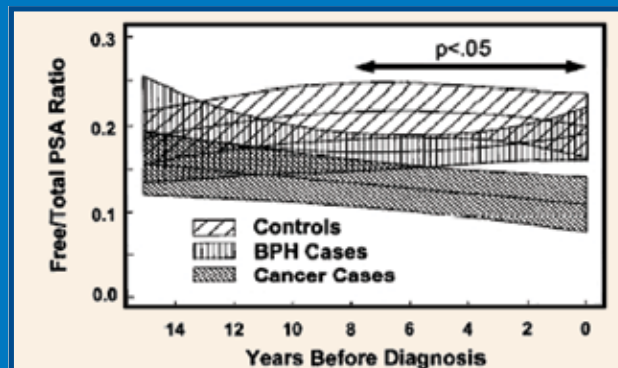


Figure 3: Importance of Serial Free to Total PSA in Forecasting PC. The value of laboratory inputs when observed over a significant span of time frequently declares the biological process. Here the free to total PSA ratio shows a gradual decline in the PC cases while this is not seen with BPH or controls. From Pearson et al.²⁶

a PSA trend showing a rising slope reflecting serial increases in Total-PSA, and then confirming that concern by seeing a Free-PSA percentage that is less than 25%, and most often in the 15% or less range. And, if a diagnosis is not established after biopsy, the physician should repeat the Free-PSA percentage (to see if this value is dropping further); if so, it would alert the physician to maintain a red alert status – and to utilize other tests that should lead to a timely diagnosis of PC.

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4.0 The Use of Nomograms and Neural Nets to Enhance PC Risk Assessment

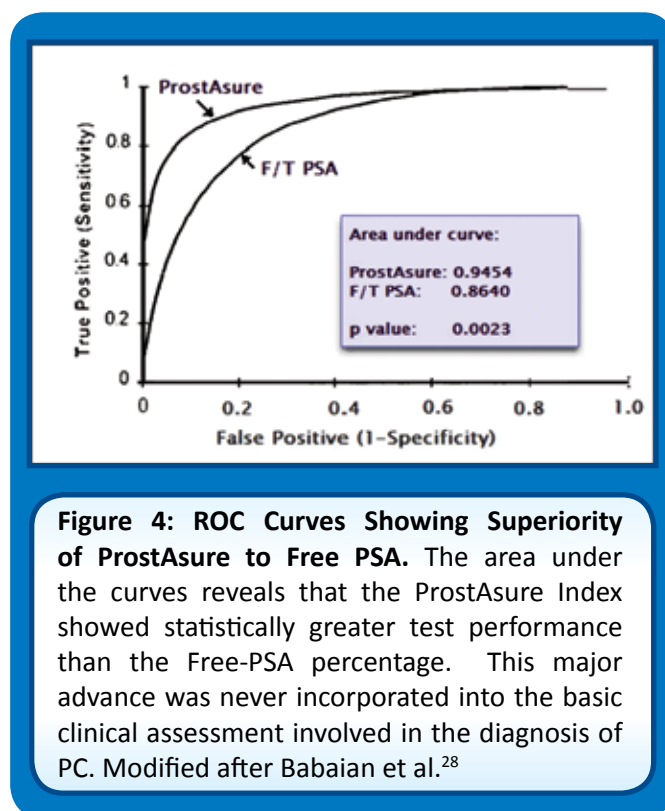
On the Prostate Cancer Research Institute website, there is a free software program (PSA II analysis within Partin/Narayan Table analysis) at <http://www.prostate-cancer.org/tools/software/pctools.html>. This enables the user to input the total PSA, Free-PSA percentage, and age of the patient and determine the probability of PC. This nomogram is based on the study by Chen et al who found a low probability ($\leq 15\%$) of PC when the Free-PSA percentage was $> 25\%$, in contrast to more than 90% likelihood of PC for men with a Free-PSA percentage of $< 7\%$ at total PSA levels between 2.5 and 20.0 ng/ml for all ages.²⁷

The nomogram that most patients and physicians are familiar with is the one by Partin et al that uses PSA, clinical stage and Gleason score to predict the findings at RP. There are many nomograms and some neural net programs that deal with the full scope of the genealogy of PC – from prevention to diagnosis, to assessment of stage and prediction of findings at RP, to determinations of local versus systemic recurrence after RP, to results of treatment modalities such as RP and RT, and to predicting results in the setting of advanced disease. These applications use a combination of clinical and pathologic findings for a particular patient to derive more statistically significant outcomes compared to what can be obtained from any single variable (biologic input).

The philosophy involved in the above mindset is “don’t hang all your hats on one hook”. D’Amico attempted to popularize the importance of nomograms with the phrase “combined variable analysis”. The topic of nomograms was discussed in great depth in the May 2001 and November 2005 issues of *Insights*. Artificial Neural Nets (ANNs) utilize a pattern recognition approach simulating the human brain. Sometimes the variables involved in ANNs may appear to make little sense, but the ANN is programmed to look for patterns associated with a particular outcome. Examples of three different ANN programs forecasting the likelihood of (1) cancer spreading outside the prostate, (2) lymph node involvement and (3) PSA recurrence after RP are available on the Internet at <http://www.prostatecalculator.org>. Check it out.

Approximately 10 years ago, Babaian et al published a highly provocative article describing the use of an ANN

called the ProstAsure Index to diagnose PC.²⁸ The patients studied were men with a total serum PSA of 4.0 ng/ml or less and a normal DRE. The input variables were patient age, total PSA, total creatinine phosphokinase (CPK) isoenzymes, and PAP (prostatic acid phosphatase). The sensitivity (true positive/(true positive + false negative)) of the ProstAsure Index was 93%. The specificity (true negatives/(true negatives + false positives)) was 81%. In this study, when the Free-PSA percentage was compared to the ProstAsure Index, it showed a sensitivity and specificity of 80% and 74%, respectively, using a Free-PSA percentage cut-off of 15% or less. A graphic portrayal of the performance of ProstAsure versus Free-PSA percentage using receiver operating curves (ROC) is shown in Figure 4. Unfortunately, this most important advance to assist in the diagnosis of PC was never realized due to lack of approval of this test by the FDA.



Babaian’s work was continued with additional training sets of data from three medical institutions, along with additional biologic inputs of Free-PSA percentage to create a new ANN called PCD-I (Prostate Cancer Detection Index). A comparison of the specificity of PCD-I with % fPSA, PSAD (PSA density), and PSAD-TZ (PSA density of transition zone) when sensitivity was held constant at 92% revealed that the specificity of the PCD-I was significantly better ($p < 0.0001$). This is shown in Table 2.

	SENSITIVITY %	SPECIFICITY %	POSITIVE PREDICTIVE VALUE %	NEGATIVE PREDICTIVE VALUE %	TOTAL BIOPSIES SAVED %
PSAD	92	43	34	94	34
PSAD-TZ	92	39	33	94	32
% fPSA	92	11	25	81	10
PCD-I	92	62	44	96	49

Table 2: Comparison of ANN PCD-I with Other PSA Enhancements. A comparison of the specificity of the various tests when the sensitivity was held constant at 92% revealed that the specificity of the PCD-I was significantly better than that of the % fPSA, PSAD, and PSAD-TZ. Modified after Babaian et al 2000.²⁹

Babaian et al noted that if the threshold to recommend a biopsy is lowered to a PSA value of 2.5 ng/mL, approximately 100,000 additional prostate biopsies would be performed annually. If PCD-I was used instead of the %fPSA, 46.8 million dollars (excluding any test charge differences) would be saved annually (39,000 biopsies/year X \$1200/biopsy). Sadly, PCD-I has never been approved for clinical use in the detection of PC.²⁹

5.0 The Use of PSA Derivatives Such As PSAV, PSADT, and PSAD

The PSA assay became commercially available for use in 1987. Within a few years of its use in the clinical management of patients, it was clear that PSA was one of the key ingredients in understanding the biologic process we call PC. Evidence for this is seen by the incorporation of PSA into virtually all nomograms and neural nets involving this disease.

What are forgotten too often by physicians and patients alike, are the basic behavioral characteristics of prostate cancer that are part and parcel of the concept of profiling. As a malignant cell population expands, it does this essentially in a geometric fashion – one cell dividing into two, two into four and so on. Cancer cells do die along the way but the basic growth pattern is geometric and is called Gompertzian growth, named after the self-educated British mathematician and actuary Benjamin Gompertz (1779-1865). Gompertz observed that a law of geometric progression was an inherent part of different tables of mortality for humans. His equation described an exponential rise in death rates between sexual maturity and old age – an essential law of mortality that was first among the reliable empirical tools for describing the dying out process of living organisms – including cancer cells.³⁰

A second feature of the cancer cell population is that it is no different than the normal cell population in its push

to elaborate a myriad of molecules that act to further the survival of each cell. Prostate-specific antigen is such a cell product with vital functions to both the normal prostate epithelial cell (it liquefies the ejaculate) and to the malignant prostate cell (it is a protease enzyme that helps break down the basement membrane to allow cancer spread). The test we call PSA involves determining PSA levels in the serum; its level(s) reflects the number of PSA producing cells (benign and malignant) and also, in the context of a malignancy, the nature of the PC population. These are the basics for explaining the utility of the tests labeled as “PSA derivatives”, which include PSA velocity (PSAV), PSA doubling time (PSADT), and PSA density (PSAD), to name three of the most important ones.

PSA Velocity (PSAV)

In the *Primer on Prostate Cancer*, we stated that a PSADT shorter than 12 years and a PSAV greater than 0.75 ng/ml/year relate to a greater probability of a malignant condition. After years of involving many patient calculations (pun intended), I would now maintain the PSADT threshold but would reduce the PSAV threshold for concern about PC to 0.3 ng/ml/year, perhaps less. I emphasize – strongly – to use many hooks upon which to hang your hat for diagnosing PC. The pitfall that is painfully obvious involves putting full emphasis on one particular manifestation of PC, be it the Total-PSA versus Free-PSA percentage, etc. Using a single biologic input is terribly disappointing when it comes to the act or art of profiling. Using PSA kinetics is only a part of the MD (medical detective) work that is the essence of the discipline of PC medicine, but for me, it remains highly valuable.

In 1992, Carter et al pointed out that the **average PSAV in men without subsequent evidence of PC was 0.02 ng/ml/yr**, while for those with BPH it was 0.1 ng/ml/yr, and for those with **PC, it was 0.3 ng/ml/yr.**³¹

(Continued on Page 8.)

In a landmark study published in 2007, Berger et al³² evaluated longitudinal PSA changes during a 10-year observation period in a screening study involving a cohort of 4,272 men without evidence of PC and a cohort of 528 men who eventually developed PC. **In those men without evidence of PC, the mean PSAV was 0.03** with the actual PSA mean levels increasing from 1.16 to 1.49 ng/ml during the 10 years. **Of the 528 men with PC, the mean PSAV was 0.39 ng/ml/yr.** In that group, the PSAV 8-10 years before diagnosis was 0.225 ng/ml/yr in comparison to 0.98 ng/ml/yr in the two years before diagnosis (Figure 5).

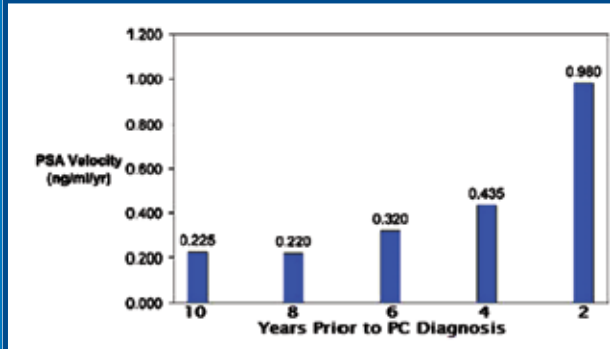


Figure 5: PSAV Prior to PC Diagnosis. The PSAV provides clues to the presence of PC many years prior to tissue confirmation by ultrasound-guided biopsy. The astute medical detective (MD) calculates the PSAV and incorporates this finding as ONE of the many profiling tools used to most accurately assess the patient’s status – all throughout the course of the patient’s illness. Modified after Berger et al 2007.³²

Berger et al’s study also showed that in men eventually diagnosed with PC, the PSAV starts to increase in the six-year period prior to diagnosis and that the PSAV was greater (median 0.53) in patients with pathologic stage T3-T4 cancer than for those with pathologic organ-confined PC (median 0.32).³² The similarities in PSAV findings between the 2007 Berger et al study and those of the 1992 Carter et al study are striking.

D’Amico et al used the PSAV results obtained one year prior to RP (radical prostatectomy) to identify men at mortality risk. They showed that a **PSAV greater than 2.0 ng/ml/yr resulted in a shorter time to death from PC** ($p < 0.001$) (See Figure 6) and death from any cause ($p = 0.01$). Additional factors that also correlated with a

shorter time to death included a Gleason score of 8-10, total PSA level at diagnosis, and a clinical stage of T2. In this crucial study, up to 28% of men died of PC in the seven years that followed an RP that was preceded by a PSAV of greater than 2.0 ng/ml/yr.³³

The value of PSAV, in my opinion, is sufficiently established by these two seminal studies. This important biologic parameter should be routinely evaluated in the profiling of patients with a major consideration being the implementation of some form of systemic therapy in those men found to be at greater risk for death due to PC.

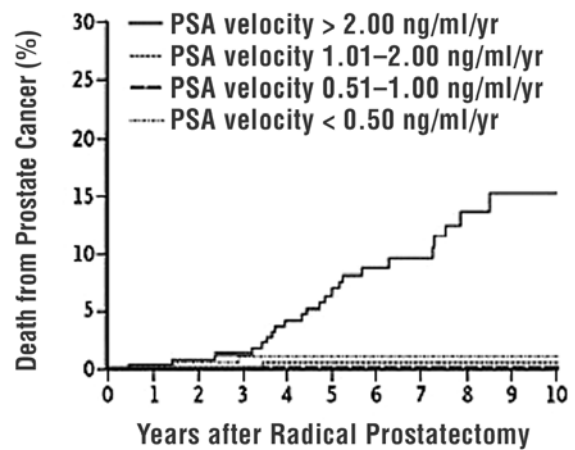


Figure 6: PSAV Correlated with Death from PC. Using the PSAV determinations obtained from testing in the year prior to RP, a PSAV greater than 2.0 ng/ml/yr had highly significant mortality implications. (modified after D’Amico et al)³³

In 2006, Berger et al published the results of their study relating pre-diagnostic PSAV to tumor volume and to subsequent PSA recurrence post-RP. Although these findings do not relate to the topic of “Diagnosis”, further discussion is warranted in the context of discussing the value of PSAV at this time. **At five years after RP, the median PSAV in men with relapse was 1.98 ng/ml/yr compared to 1.05 ng/ml/yr in men who had no evidence of disease five years after RP.** The median tumor volume in those men with recurrence of any kind post-RP was 2.55 cm³ +/- 4.17 compared to 0.94 cm³ +/- 1.23 in men without PC recurrence. The median PSAV in those with tumor volumes greater than 1.0 cm³ was 2.03 ng/ml/yr

versus 1.1 ng/ml/yr when tumor volumes of 0.51 to 1.0 cm³ were found. **The PSAV for primary tumors 0.5 cm³ or less was 0.59 ng/ml/yr.** These findings are summarized in Table 3.³⁴ It is clear that an understanding of PSA velocity is helpful to determine not only a man's risk for PC but also to assess the degree of aggressiveness that would relate to the need for intensive interaction in contrast to an approach involving non-invasive measures.

FINDINGS	MEDIAN PSAV	MEDIAN TUMOR VOLUME
Recurrence Post RP	1.98	2.55 ± 4.17
No Recurrence	1.05	0.94 ± 1.23
PC volume > 1.0 cm ³	2.03	
PC volume 0.51-1.0 cm ³	1.10	
PC volume ≤ 0.5 cm ³	0.59	

Table 3: PSAV Correlates with Clinical-Pathologic Findings. PSAV is one of the biological inputs that correlates with PC volume and PC recurrence post-RP. After Berger et al 2006.³⁴

PSA OR DERIVATIVE	AREA UNDER CURVE	STANDARD DEVIATION	95% CONFIDENCE INTERVAL
PSA	0.585	0.039	0.530-0.639
Free to Total PSA	0.749	0.031	0.695-0.798
PSA velocity	0.734	0.036	0.683-0.782
PSA doubling time	0.516	0.038	0.460-0.571
PSA slope	0.752	0.035	0.701-0.798
lnPSA slope	0.793	0.033	0.745-0.836
PSA density	0.723	0.041	0.665-0.776
PSA transition zone density	0.735	0.048	0.664-0.798

Table 4: Measures of PSA Kinetics to Identify PC. ROC (Receiver Operating Characteristic) analyses showed the lnPSA slope to be the optimal measure that best identifies men with PC who are about to undergo biopsy. After Benecchi et al ^{58,59}.

PSA Doubling Time (PSADT)

In the many thousands of calculations I have done for PSAV and PSADT, I have found consistent value by utilizing these PSA derivatives. PC cells secrete PSA and the number of PC cells obviously relates to the tumor volume as well as to the proliferation (growth) rate of the cancer cell population. It then stands to reason that any index of PSA, either rate of increase (PSAV, PSA slope, lnPSA slope) or of rapidity of doubling of the PSA amount (PSADT) can provide valuable insights about the status of the patient during the entire course of PC, from diagnosis to death. Yet rarely do I see such calculations in the medical records of PC patients, despite 25 years of work in this field. I believe that the major reason for this is the lack of an easy-to-use electronic tool that can be readily accessed by mathematically challenged physicians involved in PC care.

As this article was being submitted for publication, I was fortunate to have a collegial interchange with Luigi Benecchi. His group recently presented their findings at the AUA (American Urological Association) meeting this year in Orlando on the value of the lnPSA slope (the natural logarithm of the PSA slope). As shown in Table 4, using ROC analyses, they found that the lnPSA slope showed better results than PSA, PSAV, PSA slope and PSADT in discerning men with PC than in control patients. (Benecchi 2008 abs, Benecchi 2008 optimal measure paper ^{58,59}).

Dr. Benecchi and his colleagues from Parma, Italy have made available a very user friendly software program as an Excel spreadsheet to perform these calculations. This is available at <http://www.urologiaparma.com/lnPSAslope.htm>.

The pitfalls in these calculations relate to the need to use the same laboratory methodology (assay type)^{35,36} (1) to obtain the PSA samples either in the a.m. or in the p.m.) due to some reports of diurnal variations in PSA,³⁷ (2) to obtain sufficient numbers of sampling (*Continued on Page 10.*)

points at reasonable intervals (at least three PSA levels and ideally at six-month intervals), and (3) to ensure that no ejaculation occurs for 48 hours prior to PSA testing.^{38,39} Bicycle riding and other situations (such as those mentioned in Section 1) that may raise PSA remain controversial issues.⁴⁰⁻⁴⁹ I avoid the above issues by advising patients to defer from any potentially confounding situation and to remind physicians to obtain PSA levels prior to any manipulation of the prostate gland.

Of course, PSA-related calculations have little meaning in the setting of levels that are up and down due to prostatitis or that are lowered by 5-alpha reductase inhibitors like finasteride (Proscar) or dutasteride (Avodart). After the PSA has reached its nadir due to the use of such drugs, the PSA values then take on renewed meaning and calculations can be performed.

Most students of PC would agree that a short PSADT of < six months is correlated with highly aggressive PC and a high risk of mortality due to PC. In an Egawa et al study of established patients with PC, a PSADT of ≤ three years was associated with pathologic T3 disease at RP.⁵⁰ The impact of a short PSADT on PSA progression is shown in Table 5 in a hypothetical patient starting with a PSA of only 1.0.

In the context of using PSADT as a high risk factor for the diagnosis of PC, I do not recall seeing a single patient where multiple PSA values obtained with the same laboratory and showing a DT of < 12 years who was not eventually diagnosed with PC. Clearly, we do not have to hang all of our hats on any PSA kinetic value and **we can use multiple inputs such as Free-PSA percentage, PCA-3, DRE, family history of PC, PSA slope, and PSAV to determine if systematic and targeted biopsies should be performed.**

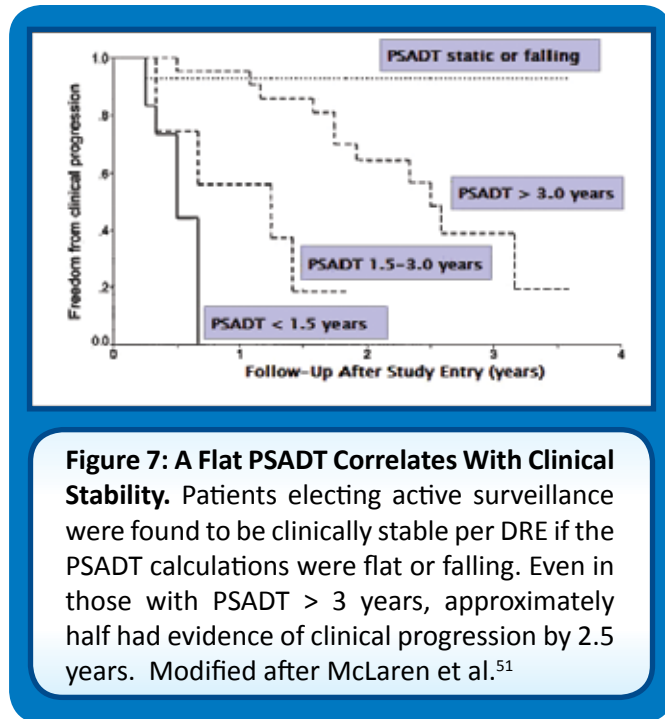
A diagnosis of PC is important to establish even if so-called definitive (potentially curative) treatment, e.g. RP, RT, Cryo, or HIFU is NOT performed. Because PC is linked with so many other medical problems that affect morbidity and mortality, an early diagnosis and appropriate evaluation of PC can result in significant improvement in the quality and quantity of a man’s life. Thus, an early diagnosis of PC becomes an impetus to look closely at a man’s status regarding bone integrity, renal disease, cardiovascular

disease, endocrine status, erectile and urine flow status, and neurodegenerative disease, to name the most important linked issues.

Most of the published studies on PSADT evaluate its value in the setting of response to local treatments such as RP or RT, or in the response to salvage therapies or treatment with ADT. In 1998, McLaren et al evaluated PSADT in the setting of observation involving 113 untreated men with PC. PSADT was found on multivariate analysis to strongly correlate with clinical progression (P < 0.0001), stage progression (P = 0.01), and time to treatment (P = 0.0001). As shown in Figure 7, approximately 50% of patients with a PSADT of < 18 months progressed within six months.⁵¹

Date	PSA	PSAV	PSADT
		ng/ml/yr	months
1/1/2000	1.0		
		0.0997	12.00
1/1/2001	2.0		
		2.000	11.97
1/1/2002	4.0		
		4.000	11.97
1/1/2003	8.0		
		8.000	11.97
1/1/2004	16.0		
		15.956	12.00
1/1/2005	32.0		
		32.000	11.97
1/1/2006	64.0		
		64.000	11.97
1/1/2007	128.0		
		128.000	11.97
1/1/2008	256.0		

Table 5: Effect of Short PSADT (12 months) on Cumulative Increase in PSA. Despite a low PSA of 1.0 in 2000, the PSA within 5 years was 32.0 and three years later it was 256 ng/ml.



More recently, Klotz et al have also used the PSADT as one of the measures to assess men in an active surveillance setting. They selected a PSADT threshold of greater than three years as one of the parameters to direct patients into the surveillance arm, while advising those with a PSADT of less than or equal to three years to seek radical intervention. The mean PSADT in their series of 231 patients was 7.0 years.⁵² Patients on the active surveillance arm had close monitoring of serum PSA and periodic repeat prostate biopsies at years 1, 4, 7 and 10 years. **In another series of patients treated in this way, 65% have remained free of treatment at eight years, and the PC-specific survival was 99.3% at eight years.**

It would stand to reason that if PSADT is being used in this manner in a context of already diagnosed PC, the same approach, or at least part of it, could be used in men where a timely diagnosis of PC is of concern. I have used this approach as part of a risk assessment “package” and find that the threshold of PSADT < 12 years works nicely along with other medical detective adjuncts (PSA velocity, PSA slope, PSAD, DRE, PCA-3, Free-PSA percentage, family history of PC or breast cancer) to help identify men needing focused studies to rule in or rule out PC. Optimizing this evaluation involves understanding the need for multiple variables (biologic inputs) to do superior profiling. **If it looks like a duck, walks like a duck, quacks like a duck, has webbed feet and feathers, then you can be pretty sure it’s a duck.**

PSA Density (PSAD)

PSAD is calculated by dividing the total PSA by the prostate gland volume. The gland volume for this determination is almost always determined by TRUSP (transrectal ultrasound of the prostate), but there are a few published articles on PSAD using the results of magnetic resonance imaging (MRI).⁵³ My experience with PSAD is that it provides another bit of information that is helpful in ascertaining whether PC may be present, as well as in giving prognostic information if one confirms a diagnosis of PC by tissue biopsies.

On the PCRI website (www.pcri.org) at the URL (<http://www.prostate-cancer.org/tools/software/tumorvol.html>) is an Excel software program that calculates tumor volume based on total PSA, PSA leak and gland volume. An integral part of this software is the calculation that the prostate gland volume x 0.067 equals the amount of benign-related PSA, (i.e. that produced by normal prostatic tissue). This benign-related PSA, subtracted from the total PSA, should equate with excess PSA – that produced by the PC, assuming that inflammation is absent. The term PSA leak takes into account the finding that as the Gleason score becomes higher, there is less PSA leaked into the blood.⁶ The excess PSA divided by PSA leak is thus used as a calculation of tumor volume.⁵⁴

I have found this quite useful and often highly consistent with the pathology findings in men who undergo RP. I believe that the concept of PSAD should take into account the contribution of the gland volume insofar as the production of benign PSA and the excess PSA that reflects the PC volume. In Table 6, we show the same PSA of 6.0 in 4 different men presenting with different gland volumes: 20 cc, 40cc, 50 cc and 80 cc. The malignant PSA divided by a PSA leak of 4.26 (presuming the Gleason score is 6) is shown as calculated tumor volume.

The PC in the small gland is of greater concern than that in the large 80cc gland for a given PSA. **But these same principles should also have relevance in relationship to the likelihood of the presence of biologically significant PC in any man concerned about a possible diagnosis of PC.** My advice is to review as many of the biologic variables that are available and to weigh their value in the context of the full picture. Is the PSAD 0.15 or higher, and if so, what about the Free-PSA (*Continued on Page 12.*)

Gland Volume	Total PSA	PSAD	Benign PSA	Malignant PSA	Calculated tumor vol
20 cc	6.0	0.30	1.34	4.66	1.09 cc
40 cc	6.0	0.15	2.68	3.32	0.78 cc
50 cc	6.0	0.12	3.35	2.65	0.62 cc
80 cc	6.0	0.075	5.36	0.64	0.15 cc

Table 6: Calculated Tumor Volume Related to Gland Volume for a Particular PSA. The calculations above are based on the finding of a Gleason score of (3,3) that has an associated PSA leak of 4.26. This is based on the work of Aihara et al.⁶ A large gland volume with a low PSAD would be associated with biologically insignificant PC using a threshold of 0.5cc.

percentage, PSADT, PSAV and ideally PSA slope? Use as many of these parameters along with family history, DRE findings, and even calculate a tumor volume based on what you might expect if PC were present, assuming the most commonly found Gleason score of 6.

For the most part, a review of the literature indicates that PSAD has value in the diagnosis of PC. Kawai et al showed that at cut-off values of 0.15 for PSAD and 25% for Free-PSA percentage, the combined use of both of these biologic inputs resulted in a sensitivity of 100% and specificity of 46.5%. That means that there would be approximately 50% false-positive impressions that PC would be present when in fact the biopsies would not show any evidence of PC.⁵⁵ A combination of PSAD of ≥ 0.15 and a PSA slope of ≥ 0.75 was related to more than a 3.5 times probability of detecting PC in contrast to values less than 0.15 and 0.75, respectively.⁵⁶ At a PSAD of 0.18 or more, a sensitivity of 70% and a specificity of 67% for the diagnosis of PC was reported by Gohji et al.⁵⁷

The tools presented represent reasonable assumptions that seem to work in the reality of the man with PC. As the PC population grows almost exponentially, so does the PSA level. This results in elevations of PSA velocity and increases in PSA slope with subsequent shortening of the PSA doubling time. As the PSA increases in the setting of underlying PC, the PSAD increases. If this goes unchecked, then the status of a normal DRE degrades into one revealing a palpable abnormality reflecting an increasing tumor volume. In time, this decreases the chances of finding organ-confined PC. What is astounding is that given the use of TRUSP since about 1985, and PSA since 1987, the above-described tools are not

used as often as they should be and the development and implementation of ANNs incorporating these variables are seldom seen.

I am hopeful that leaders in the field of ANN in PC will continue to contribute new programs that show usefulness in the diagnosis and evaluation of PC. It is planned that future installments of this series on *What We Should Have Learned About PC* will cover the topics of:

Imaging Issues in the Diagnosis (Dx) of PC

- Variability in TRUSP (transrectal ultrasound of the prostate) equipment and in the nature of ultrasound (gray scale vs color Doppler vs contrast enhanced Doppler)
- Variability in skill of ultrasonographer (choice of an artist issue)
- Need for a standard reporting format for ultrasound report
- Lack of use of endorectal MRI with spectroscopy along with lack of FDA approval of 3Tesla magnets (utility in targeting areas that need to be biopsied)

Pathology Issues in the Dx of PC

- Systematic 5-region biopsy should be mandatory
- Pathologists and Urologists fail to identify biopsy cores as to anatomic site, or even left versus right
- Need for accreditation of experts in pathology of PC
- Need for a standard reporting format for diagnostic biopsy
- Use of PCA-3 and EPCA (early prostate cancer antigen)



Stephen B. Strum, M.D. Medical Oncologist

Stephen B. Strum is a medical oncologist who has been involved in the treatment of prostate cancer for 25 years. In 1990, he founded a medical oncology practice devoted to prostate cancer and went into partnership with Dr. Mark Scholz in 1995. In 1996, the two co-founded the PCRI. Dr. Strum was the first medical director of the PCRI, as well as editor-in-chief of *Insights*.

Dr. Strum has published widely on such subjects as androgen deprivation therapy, intermittent androgen deprivation, high-dose ketoconazole, and the importance of bone integrity. In 2003, he founded a prostate cancer consulting practice in Ashland, Oregon, where he works with patients and physicians in the U.S., Canada, Europe, Australia, and the Philippines.

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**EAU
2008
CONFERENCE**

23rd Annual EAU Congress

By Douglas Chinn, M.D.

EAU Congress • Italy 26 – 29 March 2008

This year, the 23rd annual European Association of Urology conference was held in Milan, Italy, at the end of March, 2008. Professor Per-Anders Abrahamsson, Secretary-General of the EAU, announced that the annual EAU meeting is now an international meeting based in Europe, with almost 14,000 participants and over 9,000 registered attendees from over 84 countries. Although the meeting has become so widely popular at an international level, Europe will remain the focus of the EAU. Its popularity is reinforced by that fact that only 30% of the submitted abstracts could be accepted for presentation. Prostate cancer continues to be a major focus at this meeting, with multiple simultaneous sessions on multiple topics. In fact, as shown in **Figure 1**, prostate cancer represented 57% (319 of 559) of all of the abstracts accepted for urologic oncology at the EAU conference this year.

Several practical and important topics were discussed at this meeting, primarily diagnostic and surgical staging of prostate cancer. Why is this important? Again, one must remember that, with the initiation of screening programs in Europe, cancer is being diagnosed earlier, and more options are now available, namely active surveillance, focal therapy, and minimally invasive alternatives to robotic radical prostatectomy. With more accurate and reliable staging, one hopes that the ability to make an educated decision among the treatment choices is increased to avoid treatment failures, or unnecessary treatment side effects.

DIAGNOSTIC ULTRASOUND

Real-Timed Elastography (RTE) Targeted Biopsy:

An Hitachi ultrasound unit is capable of comparing the elasticity of prostate tissue. Cancer tissue is felt to be more rigid, and the higher the Gleason grade, the less elasticity is present as well. With the same applied pressure, soft tissue will deform more than hard tissue structures. (**Figure 2**) The relative displacement of each pixel is measured by tracking structures in subsequent image frames. The strain image is estimated by calculating the gradient of the displacements and is displayed as a color overlay of the B-Mode image. The more stiff structures are displayed (Continued on Page 16.)



Floor of the EAU 2008 Exhibit Area

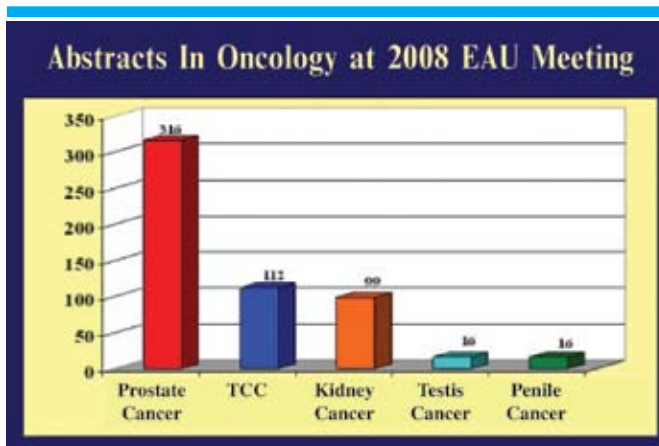


Figure 1. EAU 2008 Topics

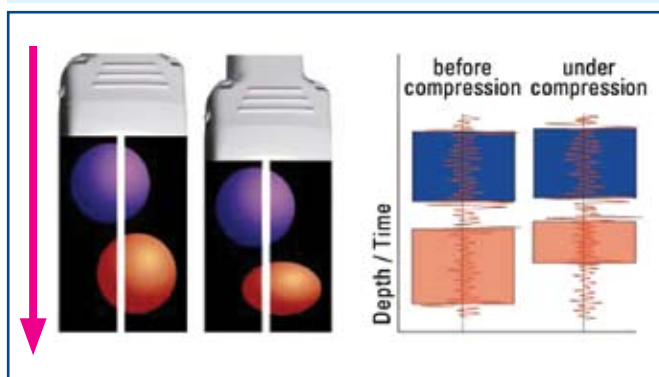


Figure 2: demonstrates the behavior of hard and soft tissue when compressed. The purple ball represents cancer and the red ball benign tissue, respectively. When the ultrasound transducer is pushed up against the prostate, normal tissue compresses, while the cancer does not, creating differential signals. The red arrow indicates the direction of the compression.

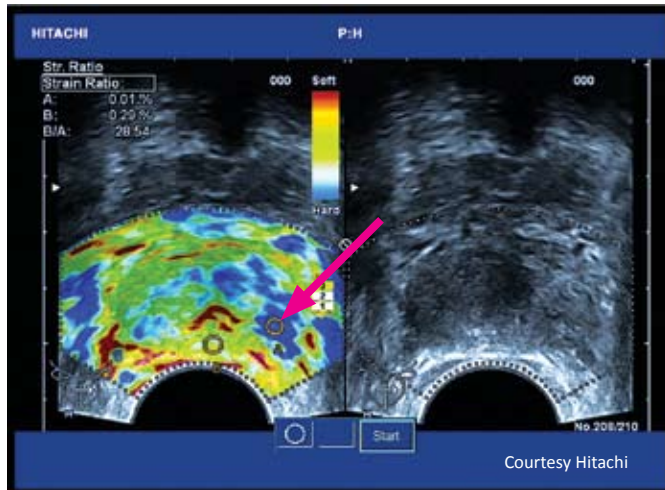


Figure 3: RTE shows a blue (stiff) lesion on the left side of the prostate (red arrow). The use of the strain ration shows a value of 28.54. Targeted biopsy revealed cancer Gleason 7.

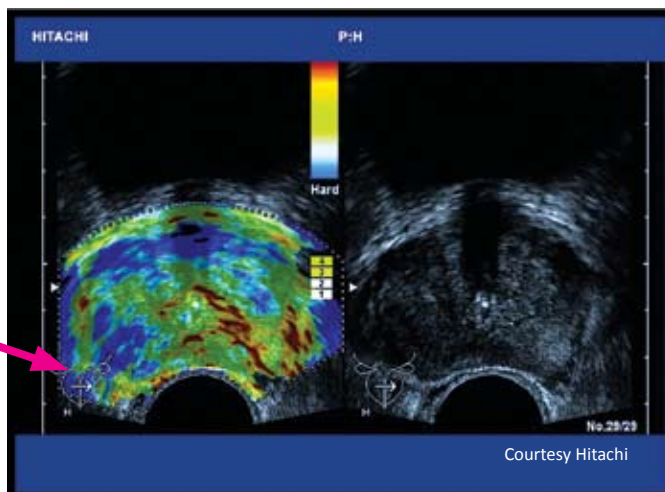


Figure 4: Cancer detected by RTE on the right side (red arrow). The capsule cannot be visualized as seen by the missing 'soft rim' sign. Pathology demonstrated extracapsular disease on the right side.

as blue while the more easily deformed tissues are displayed as red. (See **Figures 3 and 4**)

A paper presented by Pallwein et al¹ of Innsbruck, Austria discussed the role of ultrasound tissue elasticity and targeted biopsy. RTE was utilized on 383 patients, and only five targeted core biopsies were taken. Then each of these patients had a repeat standard systematic 10-core biopsy, by another urologist without knowledge of the RTE-targeted biopsy results. RTE-targeted five-core bi-

opsies detected 91.0% of the cancers, while standard systematic 10-core biopsies detected 76.9% of the cancers. Hence, the authors concluded that RTE is valuable for prostate cancer detection, with fewer biopsies. Another study was presented by Salomon et al² of Hamburg, Germany, in which 67 patients with biopsy-proven cancer underwent RTE followed by radical prostatectomy. Suspicious areas were recorded for the apex, midgland, and base areas and were compared to the findings after radical prostatectomy. A total of 212 suspicious areas were detected with RTE, and 237 tumor foci were found on the radical prostatectomy specimen (**Figure 5**). RTE appeared to be more accurate for apical cancer.

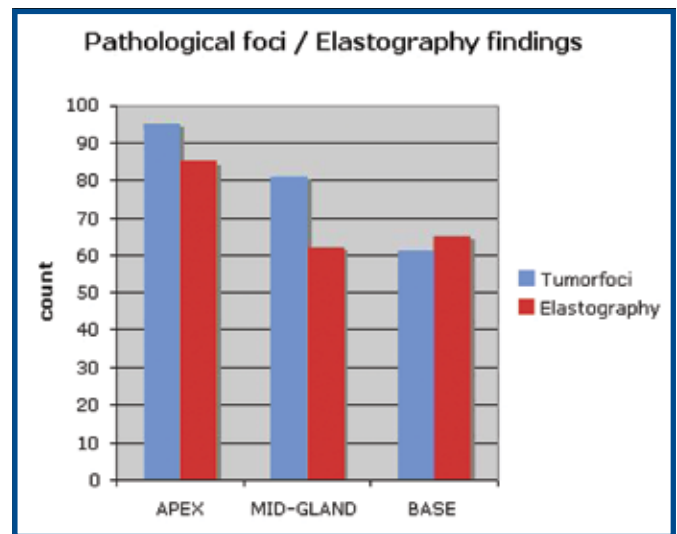


Figure 5: Comparison of tumor foci predicted by RTE and actually found. Base RTE appears to have false positive findings, in which more tumor was suspected on RTE, than what was found at the time of radical prostatectomy

RTE looks very promising as a non-invasive method to increase the accuracy and decrease the number of biopsies required to diagnose and stage localized prostate cancer. However, this technology (1) is highly operator-dependent, with a three-month learning curve, (2) has not studied transition zone cancer, and (3) benign prostatic hypertrophy and prostatitis can cause false positive readings. According to Hitachi USA, this technology is FDA-approved for the USA, and the author hopes to have access to this technology in the future.

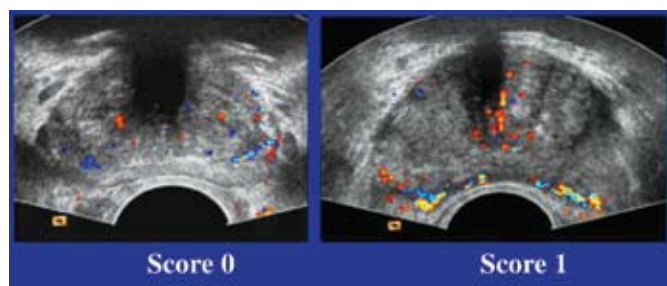


Figure 6: Scores 0 - 1

Mitterberger, et al EAU 2008

0/146 positive: 0% 10/94 positive: 11%

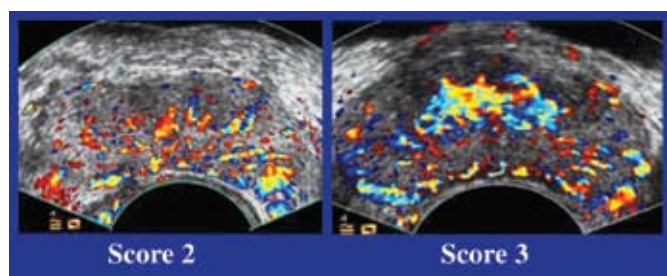


Figure 7: Scores 2 - 3

Mitterberger, et al EAU 2008

39/286 positive: 14% 42/129 positive: 33%

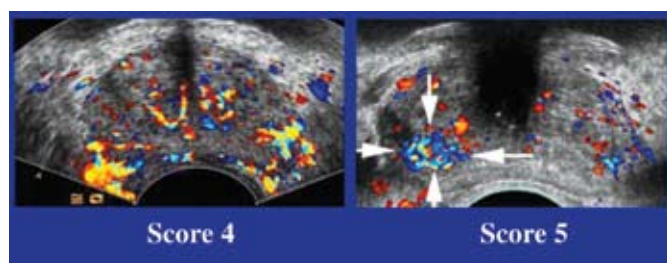


Figure 8: Scores 4 - 5

Mitterberger, et al EAU 2008

132/154 positive: 86% 114/114 positive: 100%

Contrast-Enhanced Color Doppler (Cadence Contrast-Pulse Sequence-CPS): In a study by Gradl et al³ of Innsbruck, Austria, an intravenous ultrasound contrast material called Sonovue[®] was injected into patients prior to prostate biopsy. This contrast material utilizes microbubbles to enhance the detection of increased vascularity associated with prostate cancer. Blood flow of the peripheral zone was

evaluated, and areas of earlier and stronger contrast enhancement were defined as suspicious. Twenty patients underwent a five-core, CPS-guided biopsy (Cadence Contrast-Pulse Sequence-guided biopsy), followed by a 10-core, systematic biopsy, and the results were compared. The cancer detection rates of CPS-targeted biopsy were 73% (8/11), whereas the detection rate of the standard 10-core biopsy was 40% (8/20). The difference in detection rate was statistically significant ($p < 0.001$). In patients without abnormal findings by the CPS-targeted biopsies, no cancer was detected or found with the 10-core systematic biopsy.

In another paper presented by Mitterberger et al⁴ from the same institution, 2,008 men underwent the same type of study. The number of cancers detected totaled 559 out of 2008. In total, CPS-targeted biopsies detected 23.7% while systematic biopsy detected 20.4%, which includes overlapping positive detection between the two techniques. Cancer was detected by CPS-targeted biopsies alone in 27% and by systematic biopsy alone in 15%. It also appears that contrast-enhanced ultrasound biopsies may not only decrease the number of cores required for diagnosis, but may improve the accuracy to stage the volume and location of localized prostate cancer. Once again, the results are highly operator-dependent and relied on only a subjective scoring system for rating the amount of increased blood flow identified. Finally, in a third study, Mitterberger et al⁵ from Innsbruck, Austria, developed a flow rating scale in an attempt to standardize and lessen operator variability for CPS-interpreted imaging. In this study, 923 men were screened if (1) the PSA ≥ 1.25 ng/ml, (2) a free-to-total PSA ratio $< 18\%$, and/or (3) there is a suspicious DRE. Five-core biopsies were taken of the hypervascular areas of the peripheral zone. The study team scored the enhanced Doppler ultrasound findings on a scale of 0-5, (see **Figures 6-8**) and then compared the ranked scores to the biopsy results. The flow was evaluated also for radial or abnormal, symmetrical or asymmetrical. Higher asymmetric flow was more suspicious. (See Table 1.)

As one can see, from the scoring system and the images, the evaluation is not easily standardized. However, the results appear quite consistent with the scoring system. (See Table 2)

(Continued on Page 18.)

Table 1 Flow Evaluation Results

Score	Blood Flow	Interpretation
0	Small to none	Benign
1	Some and Symmetrical	Benign
2	Slight Increase and Symmetrical	Probably Benign
3	Increased but Symmetrical	Indeterminate
4	High and Symmetrical	Probably Malignant
5	High and Asymmetrical	Malignant

Table 2 Flow Evaluation Results

Score	Number	Number positive/ Percent
0	146	0/0%
1	94	10/11%
2	286	39/14%
3	129	42/33%
4	154	132/86%
5	114	114/100%

STATUS OF PELVIC LYMPH NODES

The next major topic was the diagnostic accuracy in the staging of pelvic lymph nodes. This has been a major problem in prostate cancer, not only in the initial staging of cancer, but for treatment failures, with a ris-

ing PSA, without detectable evidence of local or metastatic recurrence. A paper published in 2008 by Hovels et al⁶ from Ulm, Germany, concluded that "CT and MRI demonstrate an equally poor performance in the detection of lymph node metastases from prostate cancer." For initial staging purposes, patients

with PSA >10, Gleason score ≥ 7 , and large volume disease are at risk to have metastatic disease. However, the disease often goes undetected by conventional imaging techniques. Patients are then often subject to localized treatment options that are going to fail, and in retrospect should have been avoided. Also, when undergoing a radical prostatectomy, the question arises: Should a patient have a simple or an extended lymph node dissection (removal of lymph nodes)? Last year, I reported an EAU finding that extended lymph node dissection detected 35% more metastatic disease than a standard node dissection, but that there may be an increase in side effects as well. The indications and extent of lymph node dissection remains controversial today, although it appears that there is consensus that patients with high-risk prostate cancer should have lymph node dissections with their radical prostatectomy. It appears that this can add another 55 minutes to a robotic procedure.

PET/CT scan: Positron emission tomography (PET) scan utilizes a radioactive tracer that can reveal metabolic changes at the cellular level and therefore may be able to detect cancer by these changes earlier or more accurately. In comparison, CT and MRI detect cancer by changes in size of the tissue, i.e. the lymph nodes. A PET scan is combined with CT, as the CT scan identifies the organ anatomy, and the PET scan identifies the metabolic abnormality, but not the anatomical structure.

18F- Fluorocholine: The standard PET scan tracer, 18F-Fluorocholine, in general has not been very helpful in prostate cancer. Steuber et al⁷ from Hamburg, Germany presented a paper describing 20 patients who underwent an 18F-Fluorocholine PET/CT scan 14 days prior to radical prostatectomy and extended pelvic lymph node dissection. Surgery revealed that 45% of these patients had positive lymph node involvement, while the PET/CT scan did not detect a single positive lymph node.

11C-Choline: Another more recent tracer is 11C-Choline. Trieber et al⁸ from Ulm and Munich, Germany, presented an abstract on the use of 11C-Choline PET/CT in detecting recurrent disease (either local or in lymph nodes) after radical prostatectomy with a rising PSA. In this study, 42 patients underwent scanning for an elevated/rising PSA after radical prostatectomy. 19/42 patients had positive scans. The detection rates depended upon PSA, and Gleason Score as noted in Table 3.

From this study, it is apparent that 11C-Choline can be helpful in localizing recurrent disease, either in the prostate bed or metastatic to the lymph nodes after radical prostatectomy. A study by Blana et al⁹ of Regensburg and Ulm, Germany presented data on patients who had a rising PSA > 0.80 and at least one negative sextant biopsy after HIFU as primary treatment. Of the 19 patients scanned, 47% (9/19) demonstrated local recurrence, and 15.8% (3/19) had positive lymph nodes. Overall sensitivity for detecting locally recurrent or lymphatic metastatic disease was 63% in this group of patients. The average PSA in this study was 2.4 ± 1.9ng/ml. (The data was not further stratified as with the Trieber study).

A paper published by Scattoni et al¹⁰ from Italy in 2007 concluded that the sensitivity for detecting lymph node involvement was 66% but the false negative incidence was 45%. In summary, 11C-Choline appears to be a very promising tracer for PET/CT scanning, and a future study similar to that of Steuber would be very enlightening. Furthermore, diagnostic PET/CT scanning might possibly help avoid choosing the wrong therapy. However, PET/CT cannot identify lesions smaller than 5mm in size. Although the scan is not 100% accurate and false negative scans will occur, it is much more sensitive than MRI and CT alone. I have been unable to locate any sites within the United

Table 3

PSA	Gleason Score	Percent Positive Correlation
<3ng/ml	<7	28%
<3ng/ml	≥7	42%
≥3ng/ml	<7	100%
≥3ng/ml	≥7	100%

States that are offering 11C-Choline PET/CT to patients on a clinical basis. It is available to patients willing to travel to Ulm, Germany.

Combix MRI: This diagnostic procedure was reviewed again this year, although no specific papers were presented. Combix MRI utilizes nano-technology iron particles that are injected into the blood stream and then taken up by the lymph nodes. On an MRI image, the lymph nodes appear “black”. If there is metastatic prostate cancer in the lymph nodes, these areas will prevent uptake of the iron particles, and there will be a “negative ghost shadow” on the MRI. This test is highly specific and can identify lesions 5-10mm in size. Currently, there is a European randomized clinical trial being conducted and it is hoped that data will be presented next year.

PELVIC LYMPH NODE DISSECTION:

Another area of controversy and concern relates to how extensive a lymph node dissection should be done during a radical prostatectomy. Is it possible to avoid completely? From the previous discussion, it is clear there is no definitive test to evaluate the presence of cancer in the lymph nodes. Therefore, at the time of surgery, a pelvic lymph node dissection is performed. However, there are two types, a standard, and an extended node dissection. The standard dissection covers less territory; therefore, fewer lymph nodes are removed for evaluation. However, more extensive node dissections can be associated with higher complications such as lymphedema (swelling) of the lower extremities and genitalia, and the procedure can add up to 55 minutes to a laparoscopic or robotic procedure. *(Continued on Page 20.)*

Sentinal lymph node (SLN):

In breast cancer, dye is intra-operatively injected into the tumor, and then the lymph nodes that take up the blue dye are removed and examined for cancer. If there is none, no further lymph node dissection takes place, again because of the complications associated with an extensive dissection. This concept for prostate cancer was discussed at the EAU. In a study presented by Weckermann¹¹ of Germany, a radioactive tracer Technesium 99 is injected into both lobes of the prostate the day before surgery. Two hours later, the patient is scanned to demonstrate the primary lymph nodes involved with lymphatic drainage of the prostate. The following day, the radioactive nodes are detected by a handheld scanner during surgery and then removed. This study found that 207/1055 (19%) men with low risk cancer had a positive SLN. Two patients in this group had a negative SLN but a positive secondary node for a false negative rate of 1%. By following the radioactive tracer during surgery, 63.3% involved nodes were found outside the region of a standard node dissection, and 15% involved nodes were found outside the region of an extended node dissection. If a sentinel node is positive, then an extended node dissection is recommended in patients with high-risk disease.

COMPARISONS WITH THE 2008 AUA CONFERENCE

One of the fascinating, yet frustrating aspects of this conference, is learning about new diagnostic and therapeutic

**Dr. Douglas Chinn**

Douglas Chinn completed his medical education at USC, and his internship and residency at Los Angeles County Medical Center. He joined the general urology practice started by his father (now retired) and brother. Dr. Chinn is a pioneer in cryosurgery for kidney and prostate cancer, and developed the patented temperature monitoring technology that is used today in cryosurgery. Dr. Chinn has published, lectured and trained physicians in cryosurgery world-wide. Dr. Chinn first studied HIFU in Europe three years ago, and now feels that its time has come.

technology that is available in Europe, but not in the United States.

Six weeks after the EAU conference, the AUA conference was held in Orlando, Florida. There were 19,000 attendees and 50% were from outside of the USA. For me, this meeting was a breath of fresh air compared to previous AUA meetings. There was a willingness to discuss new research and technology less judgmentally, much like the EAU's approach. Data and concepts were presented more in a factual and relaxed manner. There were many plenary sessions in which different aspects of prostate cancer was discussed.

In the AUA, as with the EAU, science continues to move forward, and again windows into future therapies were provided. The two most fascinating presentations were on immunotherapy and nanotechnology. While im-

munology was presented at the EAU, frankly, I could not understand the lecture, as it was way too technical as given by a PhD molecular biologist; he might as well have been presenting in Martian. Fortunately, Charles Drake MD PhD of John Hopkins was able to give a simpler presentation. The bottom line conclusion, provided by both lectures, is that Dendritic cell immunotherapy alone will not be sufficient to cure prostate cancer, and that it must be used in combination with other therapies such as GVAX vaccine or other molecular therapies. Furthermore, it is felt that immune-based therapy is best given early in patients with a rising PSA, but without evidence of metastatic disease, and when their immune system is still strong and effective.

The lecture on "Cancer Nanotechnology" by Omid Farokhzad MD of Harvard Medical School was equally fascinating

and holds much promise for the future. Basically, nanoparticles are 10⁻⁵ mm in diameter, allowing them access throughout the body. These particles are covered with a set number of receptors that specifically bind to the target cell, based upon the well documented prostate specific membrane antigen. Either within or on the surface, the nanoparticles are drugs that are toxic to the cancer cells. This way, chemotherapy can, specifically and in a larger volume, be delivered directly to cancer cells. Clinical trials are proposed to begin next year.

Finally, AUA guidelines for cryosurgery have been composed and released! In my opinion, this represents a major milestone, as there has been enough published clinical experience to convince the AUA that cryosurgery represents a therapeutic option in primary and salvage therapy for prostate cancer. In conclusion, the most exciting aspects of the EAU and the AUA and their conferences are that research continues, and is progressing, and that future new and novel treatments of prostate cancer are being based upon immunology and molecular biology. And that might hold the promise of truly curing prostate cancer. I will be looking forward to updates and new research to be presented next year.

Editor's note: Additional highlights of the AUA conference are presented in Jim O'Hard's column in the companion article that starts on page 22.

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New Technology Observed at 2008 AUA Conference

By Jim O'Hara, PCRI Educational Facilitator

PCRI was well represented at the 2008 Annual Conference of the American Urological Association (AUA) this past May in Orlando. Executive Director Mark Scholz, MD and Chief Operating Officer Joe Bueno met with exhibitors and attendees to promote PCRI and our September 2008 conference. Jan Manarite and I attended many of the sessions, while my volunteer wife Linda greeted attendees at our exhibit highlighting PCRI services.

Attended by 10,000 specialists in Urology from around the world, the AUA Conference featured 20 lectures/panel discussions, 25 courses, and over 600 abstracts highlighting prostate and prostate

cancer issues. (Some of the abstracts were reviewed by Dr. Scholz in the May 2008 issue of Insights.) The abstracts and posters are available on the AUA website and can be searched by number, author, title and subject. You only need to register at one of the following:

<http://www.abstracts2view.com/aua/>
<http://www.posters2view.com/aua08/>

I personally heard several interesting presentations and viewed many of the poster sessions. I will focus this report on some of the new technologies available for prostate cancer physicians and patients.

*Jan Manarite
& Jim O'Hara
Exhibit at AUA*



GPS for the Body®

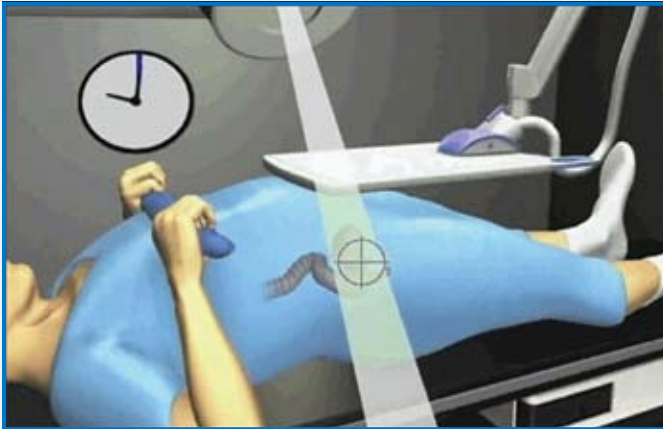


Image with permission of Calypso® Medical Technologies, Inc.

Organs naturally move during radiation treatments, and physicians cannot predict which way or how much organs will move. According to the manufacturer, Calypso Medical Technologies, its Calypso® 4D Localization System™, (also referred to as “GPS for the Body®”), enables radiation oncologists to accurately align the prostate prior to initiating each radiation treatment and then to manage any organ motion that may occur during the treatment session.

Prior to initiating external beam radiation therapy, doctors implant three tiny Beacon® electromagnetic transponders into the prostate during an outpatient procedure similar to a biopsy. Each Beacon® transponder is about the size of a grain of rice. The Beacon® transponders communicate with the Calypso System using safe radiofrequency waves during radiation therapy. The prostate position is continuously monitored during each treatment on a Calypso System display located within the treatment room. This display allows physicians to make quick, important decisions about the patient’s treatment if, during treatment, the prostate goes out of alignment with the radiation beam.

The technology is designed for body-wide cancers commonly treated with radiation therapy, including prostate, breast, lung, head, neck and other radiation therapy target organs. The products are FDA 510(k) cleared for use in the prostate and prostatic bed. Many leading cancer centers such as Fox Chase, Seattle Cancer Care Alliance, MD Anderson Orlando, and others have adopted this technology. More information is available at: www.calypsomedical.com.

* *Editor’s note:* Calypso Medical Technologies is a sponsor for the 2008 PCRI Conference.

4D Image Guidance and Navigation for Prostate Biopsy

A new imaging device, ei•Nav/Artemis™, was officially cleared by the FDA in May 2008. According to the manufacturer, the Eigen Corporation, the device offers urologists technology that will significantly help in the fight against prostate cancer. Artemis provides 4D image guidance and navigation for prostate biopsy. With the advantages of enhanced imaging, the physician will have the visual acuity to see the prostate in any dimension and to examine the prostate gland for abnormalities or any suspicious regions that may need sampling.

Artemis converts 2D Ultrasound to 3D/4D, provides enhanced biopsy-planning features, including needle navigation, and records this information for future reference. Unique to Artemis is the Atlas/HotSpot™ planning feature that is a statistical probability of known locations based on age, ethnicity, and PSA scores. Additionally, Artemis provides pre-loaded biopsy plans using conventional plans or the physician’s customized biopsy plan. During a biopsy, Artemis displays (1) the 4D orientation and navigation of the needle trajectory, (2) core position, (3) depth, and (4) deflection. With reproducible accuracy, Artemis allows the physician to view previous prostate gland volumes and biopsy locations. All of this information is recorded and saved for future reference, treatment planning and monitoring. More information is available at: www.eigen.com.

John Kurhanewicz, PhD, of the University of California San Francisco, believes that by converting 2-D ultrasound images to 3-D, Artemis provides an ability to merge high-end imaging from Magnetic Resonance Imaging and Spectroscopy with ultra-sound images. He feels that this combination should provide a significant enhancement to the ability to locate tumors and perform targeted biopsies. A prospective study is planned at UCSF.

* *Editor’s note:* Dr. Kurhanewicz was a speaker at the 2003 and 2007 PCRI Conferences and provided an article on MRI/MRSI that appeared in the November 2006 issue of Insights.

(Continued on Page 24.)

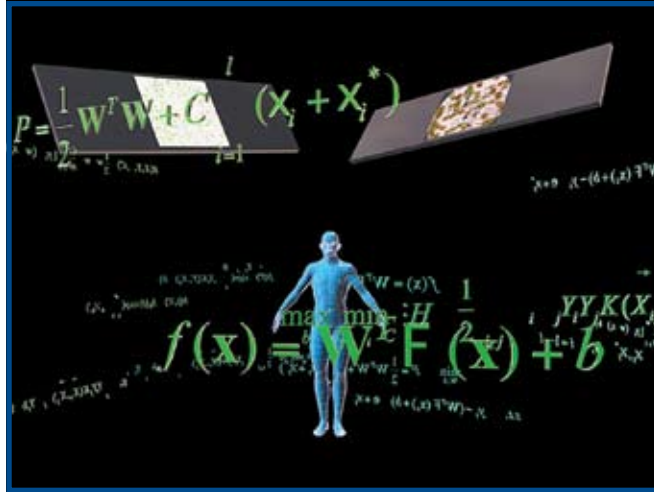


Photo Courtesy of Aureon Laboratories, Inc.

Prostate Px®

Aureon Laboratories, Inc. (a specialized laboratory dedicated to advancing personalized cancer treatment through predictive pathology) announced the introduction of Prostate Px, the first commercial test to predict prostate cancer progression and disease recurrence at the time of diagnosis. Prostate Px is designed to detect high-risk patients who present as being low-risk and undetectable by other methods. It will also reclassify intermediate-risk patients and help identify those with less aggressive disease. According to Aureon, Prostate Px is based on the results of a large study that utilized data and samples from a cohort of 1,027 men assembled from the Mayo Clinic, Uppsala University, the University of Connecticut, and the Duke University Medical Center. In validation, Aureon's predictive model identified twice as many high-risk events in low and intermediate risk patients than the previously best available method.

Prostate Px utilizes patient biopsy tissue to provide a perspective that enables more-informed decisions at diagnosis, Aureon explains. The Prostate Px "Systems Pathology" platform combines histologic, molecular, and clinical information to predict cancer recurrence by integrating three

advanced technologies: (1) digital image analysis using architectural information available at the tissue level; (2) biomarker detection using fluorescently tagged antibodies with analysis via spectral imaging; and (3) clinical information such as: Gleason score, pathologic stage, and PSA values. This advanced mathematical approach is applied to a large patient cohort to generate a personalized report that is sent to the physician for discussion with the patient. More information is available at: www.aureon.com

3D Imaging and Targeted Biopsy

According to Envisioneering Medical Technologies, its TargetScan 3D imaging and targeted biopsy system allows a physician to generate a true solid 3D image, manipulate it, and precisely plan and undertake a multi-sample biopsy of a targeted tissue mass in the prostate. The probe remains stationary during the procedure while imaging a full range of scan planes to create a 3D image in seconds. Since the position of the prostate is not disturbed by moving the probe, this both provides for more accurate sampling of the prostate's different zones and also provides better patient comfort.

A study by Andriole et al reported that “targeted transrectal biopsy specimens of the prostate were taken. The precise location of each specimen is defined by 2 coordinates: depth in centimeters proximal from the apex of the prostate, and degree of rotation (clockwise or counterclockwise from 12 o'clock)... Studies on 20 radical prostatectomy specimens disclosed that simulated TargetScan biopsy correctly identified cancer in 16 (80%) prostates and high-grade prostatic intraepithelial neoplasia in 2 others. Simulated TargetScan biopsy correctly characterized 88% of prostatic octants in terms of whether or not they harbored cancer. This technique was reproducible from operator to operator, and 85% biopsy core concordance was attained” ... The TargetScan biopsy system seems to be an effective transrectal alternative to transperineal, 3-dimensional, ultrasound-guided biopsies. Its reproducibility from operator to operator suggests that it may be useful for guiding re-biopsy of specific locations within the prostate and for providing targeted focal prostate cancer therapy.” More information is available at:

www.envisioneeringmedical.com.

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Circulating Tumor Cells

In an AUA course on High-Risk Prostate Cancer, J. Brantley Thrasher, MD discussed Abiraterone results and mentioned “circulating tumor cells”, a new marker for monitoring prostate cancer. In February 2008, Veridex, LLC announced that the FDA had granted an expanded

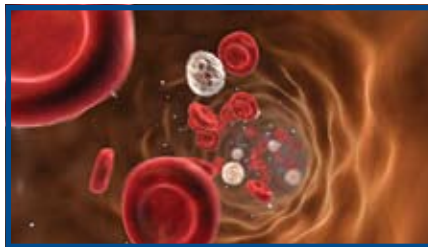


Image with permission of Ortho-Clinical Diagnostics

clearance for the CellSearch™ System to be used as an aid in the monitoring of metastatic prostate cancer patients. According to Veridex, the CellSearch™ System identifies and counts circulating tumor cells (CTCs) in a blood sample to predict progression-free survival and overall survival in patients with metastatic breast, colorectal or prostate cancer, and can do so earlier than the current standard of care.

In the Veridex announcement, Dr. Nicholas Vogelzang of the Nevada Cancer Institute was quoted

as follows: “We have compared CellSearch™ CTC test results to the standard clinical and biomedical parameters, such as prostate specific antigen (PSA) measured in metastatic prostate cancer patients. A decrease in the number of CTCs is most often associated with patients successfully responding to therapy. Further analysis of CTCs may provide information as to the most efficacious treatments for specific individuals.”

More information is available at: www.veridex.com

* *Editor’s note:* Dr. Vogelzang will be a speaker at The PCRI conference this September.

If you have questions on any of these topics, feel free to contact me via the PCRI Helpline: 1-800-641-PCRI or help@pcri.org.



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A gift to the PCRI is a special way to give tribute allowing individuals, organizations, businesses and groups to honor someone while supporting PCRI’s mission.

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Prostate Cancer

Research Institute

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Los Angeles, CA 90045

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Food For Thought

Pomegranates and Prostate Health: Research Report

Mark Dreher, Ph.D.,
Chief Scientific Officer, POM Wonderful, LLC

Fruits and Vegetables: Recognized Role in Reducing Cancer Risk

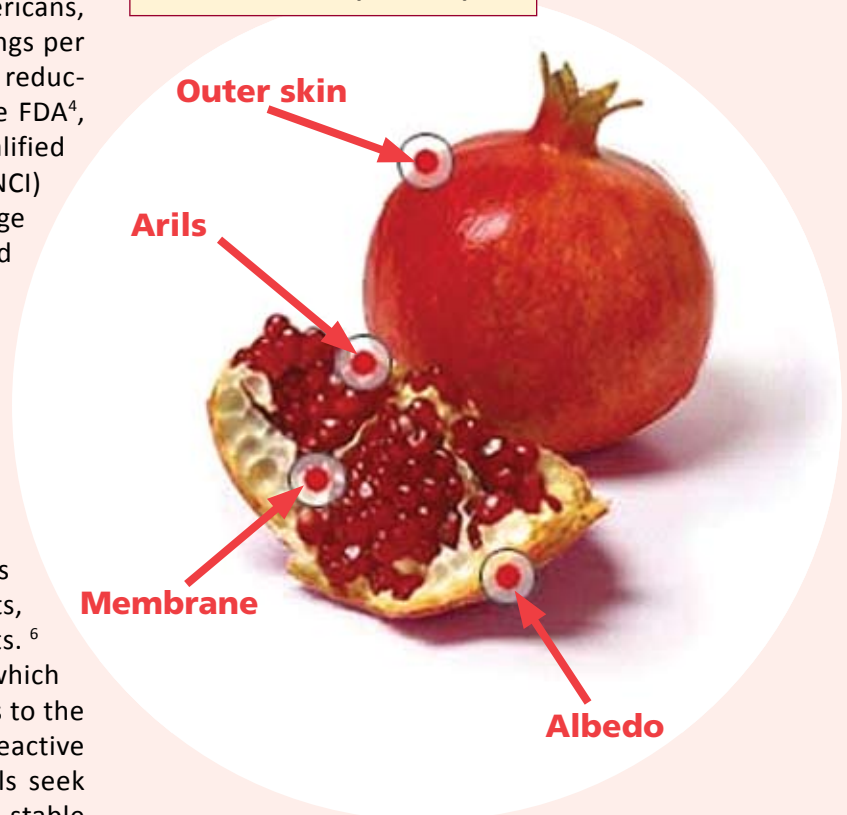
How well we age is influenced partly by our genetics but even more so by our lifestyle (e.g., eating right, exercising often, and managing stress). Since these lifestyle factors are under our control, we have the ability to influence the outcomes of some chronic diseases, including certain cancers.¹ Increasing evidence supports the important role of nutrition in cancer prevention, including prostate cancer.^{2,3} Cancer is ranked as a leading cause of death in the United States, in part because U.S. diets tend to be high in fat and calories and low in fruits and vegetables. Studies of population groups in various parts of the world indicate that diets rich in plant foods are associated with a lower risk of some cancers. >>>

Accordingly, one of the strongest U.S. authoritative dietary guidance and promotional efforts ever initiated, the “5-A-Day for Better Health” Program (now called the National Fruit & Vegetable Program), was created in 1991 in order to promote increased fruit and vegetable consumption across the nation. Additionally, the newest revision of the Dietary Guidelines for Americans, released in January 2005, changed fruit and vegetable recommendations for all Americans, increasing the number of recommended servings per day. The association of plant food intake and reduction in cancer risk has been recognized by the FDA⁴, through its approved health claims and qualified health claims. The National Cancer Institute (NCI) offers an important dietary guidance message for consumers saying that diets rich in fruits and vegetables may reduce the risk of some types of cancer and other chronic diseases.⁵ In spite of these efforts, only a fifth of Americans consume five servings or more of fruits and vegetables daily. Reversing this trend could help many Americans reduce their cancer risk.

Fruits and vegetables are a major source of nutrients and phytochemicals such as polyphenols, important natural antioxidants, which work as phyto-chemoprevention agents.⁶ The normal process of cellular metabolism, which requires oxygen from the air we breathe, leads to the production of free radicals - unstable, highly-reactive molecules that lack an electron. Free radicals seek stability by stealing electrons from other stable molecules, creating a chain reaction of free radical formation that can cause damage to body cells, proteins, and DNA if gone unchecked. Aging and/or environmental stress may enhance this oxidative stress and may also lead to chronic inflammation, which can further exacerbate damage and increase cancer risk. The polyphenol antioxidants found in certain colorful fruits and vegetables can boost the body’s natural antioxidant systems to defend against free radical damage.⁶ This antioxidant defense appears to be well suited to prostate cancer prevention because this cancer develops slowly over the course of decades (typically diagnosed in men over age 50). Research is beginning to connect fruits and vegetables to reduced risk or delay in the onset of prostate cancer^{7,8} This may help promote many years of prostate health, for even a modest delay in disease progression could significantly impact the quality of life for patients.²

Of the fruits, pomegranates (Figure 1) have been shown to promote prostate health, including possible support for prostate cancer risk reduction. This report provides an update on the latest pomegranate prostate medical research.

Figure 1. Pomegranate fruit and arils (berries)



Pomegranate Fruit: A Traditional Medicinal Remedy

The pomegranate was chosen as the logo for the *British Medical Journal's* Millennium Festival of Medicine because of its historically recognized medicinal properties.⁹ It is also featured in the heraldic crests of several medical institutions. Pomegranates were domesticated around 4,000 B.C. and the pomegranate fruit has a fascinating history of traditional use as food, medicine, and cultural icon. The fruit of the pomegranate tree has been used extensively in the folk medicine of many cultures. The healing property of pomegranates was discussed in one of the oldest medical texts, the *Ebers Papyrus* from ancient Egypt (circa 1500 BC). The fruit is mentioned in both Greek and Persian mythology representing life, regeneration, (Continued on Page 28.)

and marriage. In Judaism, pomegranate seeds are said to number 613 – one for each of the Torah’s 613 commandments. The fruit is also one of the three blessed fruits in Buddhism. In various forms of traditional Asian medicine, pomegranate fruits were recommended as a health tonic and as a treatment for numerous ailments including diarrhea, dysentery, and diabetes. For centuries, pomegranates have been used in traditional Chinese medicine as antimicrobial and anti-inflammatory agents, and the arils (pomegranate berries) symbolized longevity and immortality.

Thus, pomegranates were highly regarded for their medicinal health benefits. Over the last decade, the pomegranate has been studied by modern medicinal research methods, which are confirming an emerging multi-faceted health role. These studies have been reviewed in several books^{10,11} and by Dr. James Duke, formerly a U.S. Department of Agriculture phytochemicals expert and now Executive Director of the Green Pharmacy Garden. Dr. Duke says that pomegranate juice is his health-food beverage of choice.¹²

Pomegranates: An Emerging Role in Promoting Prostate Health

A number of review articles and chapters have summarized the emerging role of pomegranates in prostate cancer protection.^{10,13,14,15} These articles conclude that pomegranates contain promising phytochemicals for the chemoprevention and chemotherapy of prostate cancer. The most active of these compounds are ellagitannins, which are converted to phenolic metabolites such as urolithins in the large

intestine.^{15,16} These compounds have been shown to be potent antioxidant and anti-inflammatory agents.^{10,15}

Chronic inflammation has been linked to prostate cancer.^{10,11,13} Inflammation, which can result in persistent oxidative stress in cancer cells, may stimulate cancer cell proliferation and increase mutation rates through DNA damage. Oxidative stress may also increase cancer cell proliferation by increasing the sensitivity of growth factor receptors. Oxidative stress is inherent in prostate cancer cells and is responsible for many observed characteristics such as uncontrolled cell cycling and metastasis.¹⁸ Increased free radical generation may have a fundamental role in the initiation, maintenance, and promotion of prostate cancer phenotype. Products rich in antioxidant activity might help reduce oxidative stress and chronic inflammation. 100% pomegranate juice from the Wonderful variety, which contains about 2½ pomegranate fruits per serving, has been shown to contain the highest levels of polyphenol antioxidant among fruit beverages.^{15,16,19} Further, pomegranates can directly suppress NF-κB activation.¹⁰ NF-κB is thought to be a key factor in the control of cell proliferation, inhibition of apoptosis and oncogenesis in prostate cancer. A study published in the *Proceedings of the National Academy of Sciences*²⁰ provides a promising overall perspective on the role of pomegranates and prostate cancer.

Pomegranate fruit juice extract, known to be rich in pomegranate ellagitannins, was studied in mice implanted with androgen-sensitive prostate cancer cells. The research showed significant inhi-

bition in tumor growth, and a significant decrease in serum prostate-specific antigen (PSA) levels. Pomegranate extract consumption resulted in a significant drop in PSA levels or doubling time in direct relationship to prostate cancer tumor volume. Pomegranate ellagitannins inhibited PSA, a marker for prostate cancer progression. Also, *in vitro* results demonstrated that treating highly aggressive human prostate cancer PC3 cells with pomegranate extract (10-100 ug/ml) resulted in a dose-dependent inhibition of cell growth/cell viability and induction of apoptosis – programmed cell death. Also, the ellagitannins decreased PSA expression in human prostate cancer cells. The researchers concluded that “the fruit pomegranate and its associated antioxidants may possess a strong potential for development as a chemopreventive and possible therapeutic agent against prostate cancer.”

Pomegranate Prostate Cancer Research: Current Status

Editor’s Note: POM Wonderful, LLC (POM) has a comprehensive pomegranate medical research program with a focus on prostate cancer. All the following medical research was tested on POM Wonderful 100% pomegranate juice (POM PJ) or POMx extracts from the Wonderful variety grown in California by POM. POM PJ and POMx are the only pomegranate products with prostate clinical studies completed or in progress.

See pomegranatetruth.com and pomwonderful.com for more information on POM pomegranate products.

POM Research Program

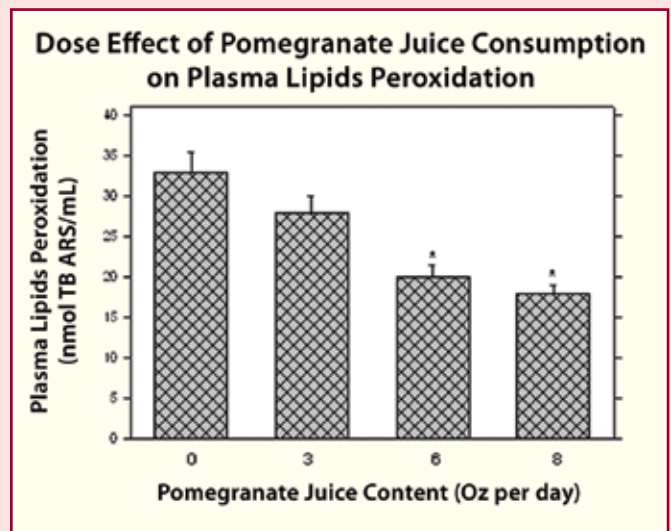
Coupled with their acquisition of pomegranate trees as part of their tree nut farming operation in the late 1980s, the Resnicks (owners of POM and Paramount Farms) began exploring the incorporation of this ancient medicinal and nutritious fruit into the American diet. In 1998, the Resnicks became the first to sponsor the scientific validation of the traditional medicinal healthful properties of pomegranates by asking Dr. Michael Aviram, head of the Technion Lipid Research Laboratory at the Rambam Medical Center in Haifa, Israel, to start research on heart health. In 2000, Dr. Aviram published the first clinical and mechanistic research on the impact of Wonderful variety pomegranate juice on atherosclerosis.²¹

In 2001, POM initiated pre-clinical research on pomegranate effects on prostate cancer for the first time with Agensys²². This research showed that pomegranate juice and extracts inhibit the proliferation of androgen-independent prostate cancer cells and angiogenesis (formation of new blood vessels important to cancer cell growth). With this basic research, a POM PJ human pilot clinical study was initiated the following year. This well-designed proof-of-principle clinical study, published in *Clinical Cancer Research* in 2006²³, suggests that POM PJ may be effective in slowing the progression of prostate cancer by extending the prostate specific antigen doubling time (PSADT) and reducing key indicators of prostate cancer development.

To date, the Resnicks have sponsored more than \$25 million in medical research ranging from heart and prostate health to common cold protection with over 20 human clinical studies completed or in progress. POM PJ research was recently reviewed by the American Botanical Council in their *Scientific and Clinical Monograph* series with a primary focus on heart and prostate health.¹⁵

lipids in the bloodstream – a key indicator of biological activity in humans.²⁴ POM PJ contains at least 650 mg of polyphenol antioxidants measured as GAE (gallic acid equivalents) per eight-ounce serving (currently POM PJ generally delivers in the range of 25-60% more than this level). With this research, POM established 650 mg GAE polyphenols as the minimum target efficacious level.

Figure 2. POM PJ Human Dose Response Study on Plasma Lipid Peroxidation



POM PJ was first launched in 2002, and this initiated the current worldwide focus on fresh fruit, pomegranate juice, and other products for their health benefits. POM currently farms 18,000 acres of pomegranate trees, which only include the Wonderful variety grown in California. POM has the only clinically tested products for prostate health.

POM PJ

Standardized effective dose. Dr. Aviram studied the dose response effects of POM PJ (Figure 2). He found that the consumption of eight ounces of POM PJ daily for two weeks can lead to a significant decline in the oxidation of

Superior Antioxidant Capacity.

A recent study compared the antioxidant potency of POM PJ to other leading brands of polyphenol-rich beverages.¹⁹ Often, a beverage will make a claim about its superior antioxidant content based on the results of one antioxidant, which can distort the true antioxidant capacity, since natural products may contain multiple compounds with varying antioxidant activity. Significant in this study is that all the beverages were tested using several methods, resulting in a more complete assessment of antioxidant activity [antioxidant potency composite index (Antioxidant Index)]. As shown in Figure 3, the Antioxidant Index of (Continued on Page 30.)

POM PJ was at least 20% greater than any of the other polyphenol-rich beverages tested.

* Wonderful variety pomegranate juice; averaged for all tests for each beverage for the antioxidant potency composite index; TEAC, Trolox equivalent antioxidant capacity; ORAC, oxygen radical absorbing capacity; FRAP, ferric reducing antioxidant capacity; DPPH, free radical scavenging properties by diphenyl-1-picrylhydrazyl radical.

POMx

POMx is the product of the pressed whole fruit after most of the juice is extracted, filtered and concentrated using juice processing techniques to produce a polyphenol-rich pomegranate juice concentrate. POMx and POM PJ have similar polyphenol components since they are produced from the same fruit. There are two forms of POMx: a serving of POMx Liquid (5 ml) or POMx Pill (1,000 mg), which are formulated to deliver at least the same target amount of active polyphenol antioxidants as an eight-ounce serving of POM PJ.

With its careful standardization, POMx has very high antioxidant potency. Internal POM data, measured by an independent laboratory, showed that POMx Pills were more potent than any other natural dietary supplement antioxidant, including red wine, grape seed, green tea, turmeric, açai, lutein, lycopene, and other pomegranate extracts.²⁵

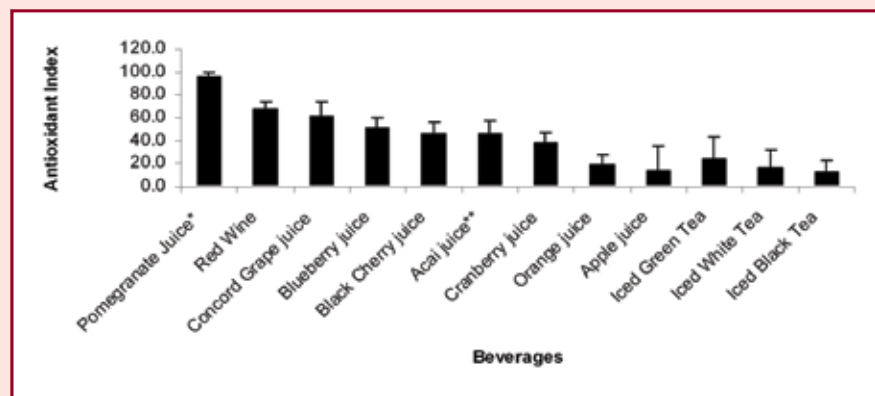


Figure 3. Antioxidant potency composite index of ready-to-drink polyphenol-rich antioxidant beverages (Antioxidant index score) $[(\text{sample score}/\text{best score}) \times 100]^*$

Human Bioavailability Research

Studies have been conducted to follow the fate of POM PJ polyphenols and their metabolites in the human body, and they have been shown to be bioavailable.²⁶ In a study conducted at UCLA, 18 healthy volunteers consumed POM PJ concentrate, and blood and urine samples were obtained to measure the levels of pomegranate polyphenols and their metabolites appearing in the blood and urine after juice consumption. One compound, ellagic acid (EA) was detected in plasma of all subjects with a maximum concentration of 0.06 mmol/L occurring one hour after consumption. EA metabolites, including dimethylellagic acid glucuronide (DMEAG) and hydroxy-6H-benzopyran-6-one derivatives (urolithins), were also detected in both blood and urine. DMEAG was found in the urine obtained from subjects 24-hours after juice consumption, while urolithin A-glucuronide took more than 48 hours to appear in the urine of subjects. These biologically active urolithins,

formed from the polyphenols by intestinal bacteria, persist in plasma and tissues and may account for some of the health benefits noted after daily pomegranate juice consumption.

A recent human clinical study confirmed similar polyphenol bioavailability profiles of the primary POM products – POM PJ (eight ounces), POMx Liquid (5 ml in eight ounces of water), and POMx Pills (1000 mg).²⁷ Tests of plasma and urine bioavailability did not show any statistical difference between the POM products. The results demonstrate that the consumption of pomegranate polyphenol antioxidants delivered by POM PJ, POMx Liquid, and POMx Pills resulted in similar absorption of ellagic acid and excretion of urolithin-A glucuronide. The same level of Urolithin-A glucuronide was detected in all urine samples regardless of the product used, reaching maximum concentrations of 1000 ng/mL, and the levels remained elevated for over 48 hours after consumption of POM products.

Human Drug Interactions

There are no known specific human drug interactions for pomegranate juice.²⁸ One member of the family of drug metabolizing enzymes, CYP3A, is thought to be the most important enzyme involved in the majority of P450-catalyzed drug metabolism. Although several *in vitro* and *in vivo* studies show a possible effect of oral pomegranate juice on CYP3A-mediated drug metabolism, these pre-clinical findings have not been confirmed in clinical research.

In one study with healthy human volunteers, it was found that pretreatment with eight ounces of POM PJ did not alter the elimination half-life volume of distribution, or clearance of intravenous or oral midazolam (drug metabolized by CYP3A).²⁸ Alternatively, the same amount of oral grapefruit juice was found to impair clearance and lead to elevated plasma levels of oral midazolam. The results of this study suggest that oral consumption of eight ounces of pomegranate juice does not alter the P450 drug metabolizing system. Further, POM PJ has been given to people with Type 2 diabetes taking oral hypoglycemic drugs for three months with no apparent negative effects on glycemic control with a significant reduction in oxidative stress.²⁹

POM Prostate Cancer Research *

Preclinical Studies

Antioxidant Activity. The potent antioxidant capacity of pomegranate polyphenols has been reported by numerous scientists using multiple *in vitro* assay systems.²²



Author Background

Mark Dreher, PhD

Mark Dreher, PhD, is the Chief Science Officer/Vice President Scientific and Regulatory Affairs for POM Wonderful, LLC, which he joined in 2005 from a position

as the Vice President of R&D for McNeil Nutritionals, a Johnson and Johnson Company. Mark received his BS degree in Biochemistry at University of California, Los Angeles, and his MS and PhD at The University of Arizona in Agricultural Biochemistry and Nutrition. Since his graduation about 30 years ago, he has held technical leadership positions in the food and pharmaceutical/nutrition industry working to advance healthy foods and nutraceuticals. Mark has authored several books on Dietary Fiber and numerous other scientific publications. He has chaired the International Life Science Institute's Food, Nutrition and Safety Committee, participated in the FAO/WHO Expert Consultation on Carbohydrates in Human Nutrition, consulted with the Institute of Food Technologists' Expert Panel on Functional Foods, and was a Fellow at the National Center for Food and Agriculture Policy.

Pomegranate juice was found to be a much more potent antioxidant in protecting nitric oxide (an important messenger molecule involved in many physiological processes within our body) than Concord grape juice, blueberry juice, red wine, vitamin C, and vitamin E.³⁰ As an antioxidant, Wonderful variety pomegranate juice was found to be 100 times more powerful than blueberry juice and 300 times more powerful than grape juice. Pomegranate juice made from the Wonderful cultivar exhibited antioxidant activity up to three times greater than that of phenolic-rich green tea and red wine. Also, animals whose diets were supplemented with POM PJ for four weeks exhibited significantly higher an-

tioxidant capacity and decreased DNA damage compared to control animals receiving their regular diet.²² Similar results have been observed for POMx products.

* POM completed all animal testing on juice as of October, 2006 and POMx as of December, 2007, and has no plans for future animal testing.

Prostate Cancer. In addition to initial POM PJ Agensys research in 2001²², POM has sponsored three additional studies on POM PJ, pomegranate extracts, and individual pomegranate polyphenols. Seeram and co-workers confirmed the Agensys findings on antiproliferative, apoptotic and (Continued on Page 32.)



antioxidant activities of POM PJ on a number of cancers including prostate cancer.³¹ This research was further studied for effects on inhibiting the growth of human prostate cancer cells as described in the following studies.

POMx Liquid supplementation was shown to inhibit prostate tumor growth by 50% when compared to control in immunodeficient mice injected with human prostate cancer cells (xenograft model).¹⁷ Urolithin-A (a bioactive metabolite of pomegranate polyphenols) is absorbed and taken up in highest concentrations in the prostate gland, and the researchers concluded that “we have shown that pomegranate ET (ellagitannins) metabolites (Urolithin A) are concentrated to a high degree in mouse prostate tissues. Given our recent observation of the effects of pomegranate juice in prostate cancer patients, the current study contributes to the increasing body of evidence demonstrating the prostate cancer chemopreventative potential of pomegranate ETs.”

POMx Pills were shown to inhibit prostate tumor growth compared to control in immunodeficient mice injected with human prostate cancer cells.³² The mice were given a POMx dose comparable to that taken by humans. POMx was shown to significantly decrease the overall blood vessel density (angiogenesis) in mouse tumors, which is important in slowing prostate cancer cell growth that is dependent upon on a blood supply. The researchers concluded that “These findings strongly suggest the potential of pomegranate ellagitannins for prevention of the multi-focal development of prostate cancer as well as to prolong survival in the growing population of prostate cancer survivors of primary therapy.”

Human Clinical Evidence

Wonderful variety pomegranate juice has been shown to increase PSA doubling time (PSADT), a measurement used to monitor disease progression and predict risk of disease recurrence. An initial proof-of-principle clinical study showed promising findings linking pomegranate juice consumption to the promotion of prostate health, specifically the prolonging of PSADT. In this study, the researchers sought to determine the effects of pomegranate polyphenol antioxidants consumption on PSA progression in men with a rising PSA following primary therapy.²³

This Phase II, open-label, single-arm clinical trial was conducted by Dr. Allan Pantuck at the Clark Urologic Center David Geffen School of Medicine, University of California at Los Angeles. It involved forty-six men (ages

are not given) with recurrent prostate cancer who had rising PSAs after treatment with surgery or radiotherapy. Eligible patients had a detectable PSA > 0.2 and < 5 ng/ml that was documented as rising before treatment. Serial PSA measurements taken before they entered the study were used to determine a baseline PSADT.

Patients were treated with eight ounces per day of pomegranate juice. Clinical end points were effect on serum PSA, as well as serum-induced proliferation and apoptosis of prostate cancer cells, serum lipid peroxidation, and serum nitric oxide levels.

Mean PSA doubling time significantly increased with treatment from a mean of 15 months at baseline to 54 months post-treatment. Serum taken from patients before and after treatment was added to prostate cancer cells that were cultured and grown in the laboratory. There was a 12% decrease in cell proliferation, a 17% increase in apoptosis, and a 23% increase in serum nitric oxide. Moreover, there were significant reductions in oxidative state and sensitivity to oxidation of serum lipids in cells treated with serum taken after treatment, compared with cells cultured with serum obtained before treatment began.

This robust, open label study was the first clinical trial of pomegranate polyphenol antioxidants in patients with prostate cancer. The statistically significant prolongation of PSA doubling time, coupled with corresponding laboratory effects on prostate cancer *in vitro* cell proliferation and apoptosis as well as oxidative stress provide

a good indication of a relationship between pomegranate polyphenol antioxidants and prostate health. Although the science has not yet reached the point of identifying pomegranate polyphenols as a treatment for prostate cancer, these studies and other evidence demonstrate the protective effects of these polyphenols in promoting prostate health.

Because of the statistically significant results experienced by many of the participants in the clinical study described above, the study was amended to allow patients to continue treatment to undergo evaluation in three-month intervals to monitor disease progression.³³ As of August 2007, seventeen (35%) active patients remained on the study with a median follow up of 30 months post-treatment (range 3-55 months). The mean PSADT for the entire cohort continues to show a significant increase following treatment, from a mean of 15 months at baseline to 58 months post-treatment. Patients remaining in the study (active) were compared to those no longer in the study (non-active). At baseline, the mean PSADTs were similar between active and non-active patients. The mean post-treatment PSADT increased in non-active patients to 51 months, but the PSADT increased to 69 months post-treatment in active patients.

The researchers concluded that “Long-term follow-up of pomegranate juice consumption in men with prostate cancer and a rising PSA demonstrates a durable increase in PSA doubling time.” The data suggest that a sub-set of patients may be more sensi-

tive to the effects of pomegranate juice. Overall, this research reaffirms the value of the earlier Pantuck research by showing that the effects can be long-term. The findings of this promising human clinical study are consistent with an underlying body of scientific evidence and have encouraged further study of pomegranate products and prostate health.

Currently, three POM-sponsored multi-center human studies including a total of about 400-subjects are in progress:

1. a 200-subject randomized, placebo-controlled clinical trial using the POMx Liquid beverage with PSADT as the primary outcome .
2. a 100-subject POMx Pill dose response study with PSADT as the primary outcome.
3. an 80-subject pre-prostatectomy human study is currently in progress to confirm the distribution of pomegranate polyphenols and metabolites in the prostate tissues.

These ongoing studies on POM products are expected to further demonstrate the relationship between the POM products and prostate health including reduced prostate cancer risk.

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Saturday night, attend the conference banquet and hear an inspiring talk by Dr. Peter Diamandis, the Founder and Chairman of the X PRIZE Foundation, an educational non-profit institute whose mission is to create radical breakthroughs for the benefit of humanity.



Dr. Diamandis holds an undergraduate degree in molecular genetics and a graduate degree in aerospace engineering, both from MIT, and an MD from Harvard Medical School. But the accomplishment that may have been most indicative of his future was when, as an eighth grader, he took first place in the Estes rocket design contest. He is the founder of the X PRIZE Foundation, which is best known for offering the \$10 million Ansari PRIZE to encourage private-sector manned spaceflight. *(Continued on page 36.)*

REGISTRATION and INFORMATION

REGISTRATION

Conference registration fees are \$85 if paid after July 31st, and \$100 if paid on day of conference. Accommodations, meals, taxes, gratuities are the responsibility of each attendee. Food carts will be available for the attendees' convenience during the entire conference.

Attendees pay separate fees for the optional Continuing Medical Education (CME) credits (\$50) and Saturday Dinner (\$40). Excursions are \$40 for the Hollywood Bowl and \$75 for the Sunset Harbor Cruise.

HOW TO REGISTER

Registration may be done by mail, phone, fax or online by visiting www.PCRI.org. Submit payments along with your completed conference registration by August 15th. PCRI accepts all major credit cards – VISA, MasterCard, American Express and Discover.

CONFIRMATION

You will receive confirmation of your registration by email if your completed registration is submitted and paid by August 15th.

CANCELLATION

Cancellations and requests for refunds will be honored through August 15th if submitted in writing by mail or fax. No exceptions.

ACCOMMODATIONS

The official hotel for the conference is the Sheraton Gateway Hotel Los Angeles Airport located at 6101 W. Century Blvd, Los Angeles, CA 90045. Call Reservations at (310) 642-1111 or (888) 627-7104 and mention Prostate Cancer Group to get the conference rate of \$109 per room per night plus applicable taxes. You will also find a link to the hotel reservation in www.PCRI.org. The special rates are available to all attendees for accommodations from September 3-10, 2008.

Please make your hotel arrangements early as the group code is valid only until August 15th after which hotel room rates will change based on availability.

HOTEL PARKING

Negotiated hotel parking rates are \$11 per day for self parking and \$22 per day for valet parking without in-out privileges.

TRAVEL

Attendees are responsible for their travel arrangements. American Airlines is providing a 5% discount on AA flights to and from Los Angeles. Call (800) 433-1790 and mention Discount Code A5498AJ or visit www.aa.com

Complimentary hotel shuttle service is available to and from hotel and LAX.

RESTAURANTS & SITES

Please visit www.PCRI.org for a list of restaurants in the vicinity.

SATURDAY NIGHT DINNER

Share a memorable evening of food, music, entertainment and fellowship with the prostate cancer community. The Harry Pinchot Awards – honoring men and women that best exemplify service, education, advocacy and excellence in the Prostate Cancer community – will be awarded on September 6.

LOS ANGELES EXCURSIONS

Consider signing up for special excursions PCRI is hosting on Friday evening and Sunday evening. (See the article on page 1.) Whether it's your first time in Los Angeles or not – make the most of it by taking advantage of this opportunity. Visit www.PCRI.org for more details.

SUPPORT GROUP MEETINGS

US T00 is holding multiple support group meetings on Saturday and Sunday. See what happens in a support group and learn what may help you and those that you care about. Sign up for these support groups. They're free to attendees.

EXHIBITS

A variety of healthcare exhibits are available on both days starting at 8:30 AM.

DONATE TO PCRI

Our continued existence and our ability to provide these conferences and other important educational materials are dependent on public support. We appreciate your generous gifts to PCRI.

ATTENDEE #1

LAST NAME	
FIRST NAME	<input type="checkbox"/> Mr. <input type="checkbox"/> Ms. <input type="checkbox"/> Dr.
ADDRESS	
CITY, ST, ZIP	
COUNTRY	
EMAIL	
TELEPHONE	

ATTENDEE #2

LAST NAME	
FIRST NAME	<input type="checkbox"/> Mr. <input type="checkbox"/> Ms. <input type="checkbox"/> Dr.
ADDRESS	
CITY, ST, ZIP	
COUNTRY	
EMAIL	
TELEPHONE	

FEES

Registration Fee	Unit Price	# of Attendees	Total \$ Amount
Regular (thru Sept 5th)	\$85		
On-Site	\$100		
Saturday Dinner	\$40		
Excursions			
___ # Hollywood Bowl	\$40		
___ # Sunset Harbor Cruise	\$75		
CME Fee	\$50		
Sub Total			

TAX-DEDUCTIBLE DONATION TO PCRI*

	Unit Price	Check One	Total \$ Amount
Patron	\$1000		
Sponsor	\$500		
Supporter	\$250		
Associate	\$100		
Friend	\$50		
Other Amount			
Sub Total			

* Please let us know if you don't wish your name included in the Conference Program

TOTAL	
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HOW TO REGISTER

Mail completed registration along with your payment to:

PCRI
5777 W. Century Blvd, Suite 800
Los Angeles, CA 90045

Or Fax completed registration along with credit card information to: **(310) 743-2113**

Or Call in your registration at telephone: **(310) 743-2117**

Or On-line at: www.PCRI.org

METHOD OF PAYMENT

- Check made payable to PCRI
 Credit Card Number **VISA • MASTER • AMEX • DISCOVER**

Security Code: _____ Exp. Date: _____

Billing Zip Code: _____

Cardholder's Name: _____

Signature: _____

Register
Online at
www.PCRI.org



He is also the co-founder and a Director of Space Adventures, Ltd., the company that has flown four private citizens on Soyuz to the International Space Station. More recently, Dr. Diamandis has created the Rocket Racing League, a cross between Indy car racing and rocket-powered flight.

Sunset Harbor Cruise

We hope you'll join us for this relaxing and fun ocean adventure on Sunday evening. Climb aboard a luxury yacht to watch the sunset as we cruise around Marina del Rey. Feel the wind in your hair and breathe the fresh sea air as we explore the local waters in style aboard a truly beautiful private charter. During this three-hour cruise, you'll also enjoy a gourmet buffet dinner prepared on board by the chefs.

To sign up for one or more of these excursions, use the form in this issue or contact the PCRI by telephone at 310-743-2117 or on-line at www.pcri.org to register.

Don't miss the boat! Be sure to attend the entire program that's being held at The Sheraton Gateway Los Angeles Hotel on September 6 and 7, 2008.



PCRI **Insights**

Published By

PCRI

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PROSTATE CANCER HELPLINE

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