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Dear PAACT Member:

For the past 25 years, it has been our pleasure to send you the PAACT Prostate Cancer Communication newsletter. During this time, we have relied solely on voluntary contributions to cover the expenses incurred in doing so.

Unfortunately, we feel that many of our members may have acquired the unfortunate attitude of letting their neighbor keep our doors open. Therefore, effective immediately, with this issue, we are pleading with you to contribute the tax-deductible amount of $50 annually, any amount will be appreciated, to receive the PAACT Prostate Cancer Communication newsletter. Also, if you were not already aware, we are available to assist you by telephone, mail or e-mail. Our sole purpose is to help men with prostate cancer; either find a cure or extend their lives as long, and by the least invasive means possible. We attempt to continually keep up with the latest methods available and pass them on to you, along with the names of doctors and institutions or hospitals.

It always saddens us to lose a member (subscriber). However, many including our founder Lloyd Ney have passed away in spite of our efforts, yet have written the nicest and kindest letters before doing so.

We understand that the economic times are difficult for all of us. Please understand that your services will not be interrupted for any reason, especially not for financial difficulties. If you are able to contribute, you will be investing in your neighbor’s future, along with your own.

With best wishes for you and your family,

Richard H. Profit, Jr. (Rick)
PAACT President
PAACT (Patient Advocates for Advanced Cancer Treatments) celebrates its 25th anniversary this year, 2009. For 25 years we have been helping those with prostate cancer and other related prostate problems through: our Prostate Cancer Communication (PCC) quarterly newsletter, verbal consultations, what we have ‘coined’ initial patient packages and whatever other means necessary and/or available. In honor of our 25th anniversary, we have changed the front cover of our Prostate Cancer Communication newsletter and will use this cover throughout 2009. 25 years in the non-profit sector makes PAACT the oldest organization and one of the largest ever to carry on this type of patient oriented information for all stages/development of prostate cancer.

Mrs. Lloyd Ney, Sr. (Janet) has announced her retirement from PAACT as President and Chairperson, which she has held since Lloyd’s passing in August, 1998. Janet will stay on as a member of the board of directors and remain active with PAACT’s operations. Assuming Janet’s position will be her son, Richard H. Profit, Jr. (Rick). Rick has been the Director of PAACT and a board member for the past 9 years.

We are also pleased to announce the addition of two new board members, Mrs. Janette Ney (Lloyd and Janet’s daughter-in-law) and Mr. Saleem Durvesh. Together, Janette and Saleem will bring a wealth of experience and knowledge ranging from business to international marketing; a perfect blend and mixture in addition to the vast experience and knowledge that our current board members already have.

We would also like to announce the addition of Mr. A.W. (Bud) Irish as an honorary board member. Bud passed on April 25, 2006. His passion for life and his desire to live served as an inspiration to many others who battled cancer. He spent the majority of his time during his retired life as an advocate for PC patients. PAACT will always be in debt to Bud for all he has done for PAACT, our members and PC patients around the world. Bud is survived by his lovely wife Elaine and family.

PAACT would also like to present, with great pleasure, the acceptance of three new members to our medical advisory board. They are: 1.) Douglas O. Chinn, M.D. with Chinn Urology in Arcadia, CA. Dr. Chinn is a specialist in Urology, Cryosurgery, and HIFU (High Intensity Focused Ultrasound) 2.) Gary E. Leach, M.D. with Tower Urology in Los Angeles, CA. Dr. Leach is an expert in incontinence. 3.) Ash Tewari, M.D., M.C.H. at Weill Cornell Medical College, in New York, NY. Dr. Tewari is a professor of Urologic-Oncology and is the Director of Robotic Prostatectomy and Urologic Oncology Outcomes. With the addition of these 3 top notch experts in their fields we will be able to keep you, the members of PAACT more informed by now having the privilege of direct contact and access to even more doctors and treatment modalities.
PROSTATE-SPECIFIC ANTIGEN (PSA) TESTING ACROSS THE DISEASE CONTINUUM
By Mark R. Haythorn¹ and Richard J. Ablin¹²

¹The Robert Benjamin Ablin Foundation for Cancer Research, Tucson, AZ 85705 and ¹²Department of Immunobiology and Pathology, University of Arizona College of Medicine, Arizona Cancer Center and the BIO5 Institute, Tucson, AZ 85724

Correspondence: Dr. Richard J. Ablin, Department of Immunobiology, University of Arizona College of Medicine P.O. Box 245221, Tucson, AZ 85724 Telephone: 520-626-7755, Facsimile: 520-626-2100, E-mail: ablinrj@email.arizona.edu

Introduction and Rationale
Prostate-specific antigen (PSA) is prostate-specific, not cancer-specific; and an elevation in the level of PSA may be due to any abnormality of the prostate. It thus remains perplexing that 35+ years after the demonstration of these facts, so many men and their physicians place such tremendous emphasis on the “absolute” PSA number determined from their latest PSA test! In order to appreciate this phenomenon, it is essential to take a step back, albeit brief, and examine how we have arrived at the current over-reliance on PSA screening and also possibly on PSA as a surrogate endpoint for the clinical efficacy of the treatment of prostate cancer.

Enigmatic, prostate cancer presents a wide variation in the age of onset of disease perhaps not seen in any other cancer. And, while the rates of clinical prostate cancer vary among global populations, the incidence of latent prostate cancer is for the most part, fairly constant.

The foregoing suggested early on in the initial investigations of prostate cancer by one of us (RJA), the possible existence of a baseline of early microscopic cancer that is accelerated to different degrees in accord with endogenous and/or exogenous tumour-promoting influences.¹ A number of studies, including those of RJA have since been directed toward the identification of tumour-promoting influences in the prostate. In concurrent investigations, attention was directed to various biological markers associated with prostate cancer. The rationale was that the identification and the quantification of tissue- or cell-type specific markers may provide insight into the diagnosis and malignant potential of prostatic tumours.

Background
Recognition in the late 1970’s of the limitations of immunoassays of prostatic acid phosphatase (PAP), one proposed tissue- or cell-type specific marker, to provide a means for the early diagnosis of prostate cancer, redirected the collective attention of several investigators to a prostate tissue-specific antigen previously demonstrated to be distinct from PAP. Identified in the normal and pathologic human prostate and its secretions, this antigen was the forerunner of the subsequently purified and characterized antigen named prostate antigen, and ultimately prostate-specific antigen (PSA).

PSA and the PSA test, almost or perhaps even more commonplace “…among men as the measurement of cholesterol,”¹² has revolutionized the practice of urology.

PSA was discovered in 1970,³⁴ and as per its namesake – PSA, was demonstrated to be prostate-specific, but not cancer-specific.⁵ On the basis of its specificity for the prostate, PSA was initially used to monitor the response, i.e., evaluate the prognosis, of the treatment of prostate cancer. Zealousness over the prospect of a blood test to determine the presence or absence of a disease, in spite of its absence of cancer-specificity, led many to the ill conceived use of the PSA test for the screening of prostate cancer. Buoyed by clever marketing of the PSA test manufacturers, the media and hopefully well intended, but ill informed urologists, screening has proliferated to “a fervour which would not disgrace a medieval inquisition.”⁶

Federal Drug Administration (FDA) Approval
In 1986, on the basis of its specificity for the prostate, the FDA approved the subsequently developed PSA test⁷ for monitoring disease status in prostate cancer patients as an indicator for the recurrence of cancer. However, the subsequent FDA approval of the PSA test in 1994 for aiding in the detection of prostate cancer, given prior knowledge that PSA is
not cancer-specific and therefore is not diagnostic of prostate cancer, was ill conceived. Additionally, the FDA did not undertake a rigorous evaluation of the clinical assay/technique and retrospective validation studies for disease detection. Furthermore, the FDA never did prospective validation studies for disease detection and prospective clinical utility assessment studies, i.e., they never evaluated the benefits and risks of PSA testing. Nonetheless in the intervening years there have been well over 10,000 publications on the PSA test and its use for screening and diagnosis of prostate cancer. In fact, some of the same investigators, who, following Ablin’s initial observations that PSA is not cancer-specific, were involved in the subsequent increase in the use of the PSA test for the screening of prostate cancer.

Interestingly, although given the FDA’s approval of the PSA test for monitoring and detection of prostate cancer, they presently do not recognize PSA as a valid surrogate endpoint for clinical efficacy in the treatment of prostate cancer.

**Screening**

A continually stated motivation for PSA screening is that the incidence of prostate cancer continues to rise. This is a flawed statement in that the incidence of prostate cancer appears to continue to rise because we are screening for an age-related disease with a test that is not cancer-specific; elevated PSA may merely reflect the growth of the prostate and is thus not accurately detecting prostate cancer.

By ‘screening’ we are referring to random PSA testing in a population of asymptomatic men – but those men with a family history of prostate cancer or those with other risk factors or symptoms should have regularly scheduled bi-annual PSA tests as one part of a diagnostic regimen. Parenthetically, PSA screening does not meet the criteria that mass screening tests should fulfill before they are applied to populations as set by the World Health Organization.8

The ability of the current commercially available PSA test used by clinical laboratories to identify men at risk for prostate cancer is slightly better than that of the flip of a coin. This is because, as an age-related disease, 45-65%9 of the men screened between the ages of 50-70 years old have latent (histological) asymptomatic prostate cancer and will die with prostate cancer, not because of prostate cancer. By and large the majority of the screen-detected prostate cancers are indolent or clinically insignificant cancers that do not alter patient mortality nor warrant aggressive treatments, e.g., by radical prostatectomy and/or radiotherapy.

A single screening test for PSA for asymptomatic men is not useful due to the inaccuracies of the testing methodology (See Section: “Shortcomings”) and confounding factors that might raise or lower PSA such as: hormones, NSAIDS, statins/cholesterol, obesity, size of the prostate, age, inflammation and/or benign prostatic hypertrophy (BPH). No PSA value has been shown to be definitive for prostate cancer.10 Additionally, there is an intraindividual variation in a single PSA determination of 16% (ranging from 15-24%).11 Thus while absolute PSA values are not meaningful, the relative change in PSA levels over time, i.e., PSA kinetics (See following Section: “Use in Disease Monitoring”) is useful in evaluating disease progression or recurrence.

The generally accepted normal range of PSA initially arbitrarily set from 0-4.0 ng/ml has subsequently been found in light of the recent Prostate Cancer Prevention Trial (PCPT) to be erroneous. Prior to the PCPT a PSA > 4 ng/ml typically indicated the need for further testing to rule out other conditions such as BPH, or this PSA level may have been an indication for the need of a biopsy. Using the initial arbitrary criteria, the positive predictive value (PPV) in a patient with PSA between 4-10 ng/ml was approximately 25%, and when PSA was > 10 ng/ml, the PPV was around 60% - just slightly better than the toss of a coin. In the PCPT a surprisingly large number of men with a PSA < 4.0 ng/ml had a diagnosis of prostate cancer, including men with a PSA as low as 0.5 ng/ml. Twenty-seven percent of patients with a PSA between 3.1 and 4.0 ng/ml were found on biopsy to have occult prostate cancer.12 Occult cancers are small or ‘hidden’ cancers that are found during a biopsy or other laboratory test, and one cannot know if occult prostate cancers are clinically relevant or if they would remain dormant or indolent. The results of PCPT established that the PSA levels below the arbitrary cutoff of 4.0 ng/ml inac-
accurately categorized some men as being normal, and those above the cutoff mischaracterized some men as being abnormal. Therefore, no one level of PSA is maximally sensitive and specific, which allows for both false-positive and false-negative results within the heretofore arbitrarily established threshold or ranges of PSA > 4 ng/ml, but rather a continuum of prostate cancer risk at all values of PSA. The results of the PCPT further illustrates the absence of the specificity of PSA for prostate cancer and the inability of the PSA test to detect prostate cancer, with the exception being that extremely high numbers (double-digit to quadruple-digit) would be indicative of an extraprostatic source of PSA, i.e., metastasis.

Other instructive observations on screening for prostate cancer may be gleaned from: 1) a model of screen-detected localized prostate cancer and the effect of radical treatment on survival and 2) the impact of screening, treatment and prostate cancer mortality in a 15-year study.

In the first, Parker, et al., noted the predicted absolute 15-year overall survival benefit for radical vs. conservative management was 1-2%. In the course thereof, patients are faced with up to 30% and 30-60% risks of treatment-related incontinence and impotence, respectively. In the second, Lu-Yao, et al., evaluated the comparative effectiveness of screening and treatment on prostate cancer mortality in Seattle and Connecticut, where the intensity of screening and treatment, with radical prostatectomy or radiotherapy, was higher in Seattle. Over a period of 15 years the adjusted rate of prostate cancer-specific mortality was 1.02 in Seattle vs. Connecticut, indicating the higher intensity of screening and treatment “...did not translate into any further reduction in prostate cancer mortality for men over age 65.”

In spite of the foregoing and what would seem to be the logical rationale against the usefulness of PSA screening, it remains controversial. Organizations that have taken a position for or against screening include:

**Advocate**
- American Cancer Society
- American Urological Association

**Do Not Advocate**
- United States Preventive Services Task Force
- American College of Physicians
- American Society of Internal Medicine
- National Cancer Institute
- American Association of Family Practitioners
- American College of Preventative Medicine

However, if one has one or more immediate family members with prostate cancer, there is an increased risk of developing prostate cancer and thus for these men it may be prudent to check PSA levels every 6 months starting at age 45, watching for relative changes in PSA over time.

**Use in Disease Monitoring**

Patients who have had their prostate surgically removed should logically have a PSA of zero, since they have no prostate. If a man has a rising PSA following prostatectomy, radiation therapy, or cryosurgery, it tells us that there are cells of prostatic origin still in the body, still producing PSA. These cells may be remnants from a prostate that was not 100% removed, or they may be prostate cells that migrated – perhaps circulating in the bloodstream or metastasizing to other sites in the body. The use of the PSA test for monitoring, as opposed to screening, may provide important insight about disease progression or recurrence provided clinicians use these data appropriately. PSA kinetics, or rate of changes in PSA levels over time, may tell us something is wrong and needs further evaluation and are more important prognostically than the absolute PSA value. Common measures of PSA kinetics are PSA velocity (rate of increase in PSA) and PSA doubling time (how long it takes for the amount of detected PSA to double in quantity). Patients and physicians need to understand the limitations of the PSA test and should not put too much emphasis on PSA numbers, and little, if any on a single digit random determination.

Monitoring PSA as a means of determining response to drug therapy is complicated by the idea that PSA expression changes as the disease progresses from
hormone-sensitive to hormone-insensitive (androgen independent) prostate cancer. In 1993 Kelly, et al., stated that patients with hormone refractory prostate cancer (HRPC) with a greater than 50% decline in PSA had increased survival, and speculated that PSA reductions could be a valid surrogate endpoint in clinical trials for HRPC. However, Verbel, et al., more recently conducted a study that showed the association between PSA and survival in HRPC is only 17%, indicating that PSA is not a valid surrogate.

Normal PSA secretion is under hormonal control. Hormonal drugs such as finasteride or leuprolide down regulate PSA mRNA, leading to a decrease in PSA that may not correlate with an effect on cell growth. Conversely, chemotherapeutic agents used for hormone refractory or castrate resistant prostate cancer may have no effect on PSA levels but could have an effect on cell growth. Prostate cell production of PSA is variable and the presence of chemotherapy alters the per-cell secretion of PSA.

In other words, using the PSA number to determine if a drug therapy is or is not working is limited in usefulness and one must be careful to not focus solely on the PSA test number, as so many men do. However, patients on hormonal therapy who have 2 or more consecutive PSA rises may be considered hormone-refractory. HRPC patients on drug therapy should not expect a consistent and reliable reduction in PSA, though rapid rises in consecutive PSA measurements (i.e., PSA kinetics) may indicate the need to further monitor for metastasis.

The primary clinical trial used for the FDA approval of Taxotere, the TAX327 study, showed an effect on overall patient survival but no clear correlation of PSA levels with survival. Armstrong, et al., showed a “moderate surrogacy effect” for PSA in patients treated with Taxotere plus estramustine but concluded that “PSA declines...are not sufficiently rigorous to be guides for modification of treatment.” Estramustine has hormonal activity, and thus one would predict that any PSA declines seen in this study are influenced by the use of estramustine.

Additionally, clinical studies of new drugs like the hormonal agent abiraterone show significant effects on PSA, but thus far we do not know if the drug will significantly impact patient survival. Several non-hormonally-acting drugs in development for HRPC, such as zibotentan or Avastin, appear (pending additional clinical data) to have an effect on patient survival but may have minimal or inconclusive effects on PSA.

It is crucial for both patients and physicians to understand that PSA absolute numbers have limitations on their usefulness, and that PSA monitoring as a means of predicting effectiveness or response to drug therapy is of limited value, particularly in hormone-refractory disease. Consecutive rising PSA levels in patients on hormone therapy can indicate androgen independence but are only one piece of data used for clinical decision-making.

**Shortcomings**

In addition to the fact that PSA is not cancer specific, current PSA assays are flawed beyond the generally known confounding factors, such as elevations in the serum PSA of patients with benign prostatic hypertrophy (BPH) in the ageing male and other irregularities of the prostate (i.e., infection and/or chronic inflammation), resulting in false-positive tests in up to 80% in some studies. Therefore, with limitations on its usefulness for screening, various PSA-related concepts evolved in an effort to enhance the performance of PSA in discriminating patients with early prostate cancer from those with BPH and other prostatic irregularities. These have included PSA density, PSA bound to alpha1-antichymotrypsin (PSA-ACT), free PSA (f-PSA), and age-specific PSA. These, as explained below, have proved inadequate.

To appreciate the reason for the inadequacy of the various PSA-related concepts, it is important to recognize that PSA exists in three major forms in serum. These are free PSA (f-PSA), PSA complexed to the serine protease inhibitors alpha1-antichymotrypsin (PSA-ACT) and alpha2-macroglobulin (PSA-AMG). Complex formation between PSA and AMG results in encapsulation of PSA and complete loss of PSA epitopes, i.e., the site that combines with the specific antibody to PSA in the PSA test that provides the means to measure the level of PSA. Therefore, current commercially available immunoassays detect only f-PSA and PSA-ACT. Consequently, what is
currently referred to as total PSA (t-PSA) is comprised of f-PSA and PSA-ACT.

The avidity of binding studies of PSA to ACT and AMG following the addition of PSA to blood plasma shows preferential complex formation between PSA and AMG, with PSA reacting with AMG about 20 times more rapidly. The formation of a stable complex between PSA and AMG results in a loss of PSA immunoreactivity. This results in a loss of PSA available for quantification by current commercial assays and incorrect calculation of the level of PSA available, whether free or in complex with ACT.

In order to have an accurate determination of t-PSA, the fraction of PSA-AMG must be included. The absence of the inclusion of PSA-AMG in what is presently considered t-PSA may be a contributing factor to discrepancies between a patient’s level of PSA and his disease status. For example, 25-33% of prostate cancer patients detected by digital rectal exam and up to 40% of patients with organ-confined prostate cancer have PSA in the normal range. Furthermore, as PSA complexes with AMG, any concomitant underlying pathology contributing to dyscrasias (abnormalities) in AMG could conceivably affect the amount of PSA available for quantification by current assays.

With current assays for PSA, the actual amount of t-PSA is underestimated. And, in instances where the ratio of PSA-ACT: t-PSA is utilized, e.g., to discriminate between BPH and prostate cancer, some patients may actually have lower ratios than had the t-PSA included quantification of PSA-AMG. Similarly, attempts to use the percentage of f-PSA, calculated as the ratio of f-PSA: t-PSA multiplied by 100, to provide improved discrimination between BPH and prostate cancer, will be flawed, in the absence of the inclusion of PSA-AMG in what constitutes t-PSA.

Age-specific PSA reference ranges, initially thought to be useful, are also inadequate in view of recent knowledge that there is no true PSA threshold for identifying prostate cancer risk as there are a significant number of men with cancer and PSA values < 4.0 ng/ml.

Thus for screening, PSA-related concepts do not work, as the basis on which they are determined are flawed. Additionally, they cannot do what they are purported to do, due to the “specificity” of a test which has no specificity for prostate cancer.

Nomograms, i.e., paradigms comprised of the PSA level, Gleason score and clinical stage have been purposed to be useful in predicting disease recurrence, metastasis or other outcomes. However, due to the shortcomings with the PSA test, as noted above, those nomograms that rely significantly on absolute PSA would be expected to be less reliable than those using PSA kinetics or those that place a lower emphasis on PSA vs. other variables.

It should be noted that the expression of PSA and cell growth are independently regulated functions in prostate cancer. Therefore, a therapeutic agent should not be assumed to have:

- An effect on tumor cell growth because it down-regulates PSA expression/secretion or,
- No effect on tumor cell growth because it up-regulates PSA expression and secretion

Therefore changes in PSA following treatment may not accurately indicate the presence or absence of a drug response.

**Over Diagnosis and Over Treatment**

Because of the absence of the specificity of the PSA test and flawed PSA-related concepts for prostate cancer, most staged cancer detected by PSA screening is microscopic and results in an estimated 56% overdiagnosis and overtreatment with attendant morbidities of incontinence, impotence and even recurrence of disease, which in some instances is worse than initially diagnosed. This contrasts with Klein’s opinion, who states that 92% of prostate cancers detected by PSA screening are localized, clinically relevant and curable. If Klein is correct, then:

- Why is there a 25-35% recurrence within 5 years following treatment?
- Why do 20-30% of the patients with localized prostate cancer, who received so-called “definitive treatment,” develop metastatic disease?
• And, even more perplexing in quoting Catalona, who has recently advocated lowering the threshold for a level of PSA to 2.5 ng/ml indicative of a biopsy “…we do not yet have definitive data that early cancer detection via screening with any PSA cutoff improves patient outcomes.”26

Relative to Catalona’s proposal, we hasten to remind you that there is no true PSA threshold (cut-off point) for identifying the risk of prostate cancer. And, with a reduction to a threshold of 2.5 ng/ml, an additional 1.8 million men between the ages of 40-69, to the already 1.5 million labeled abnormal men aged 40-69 years using the level of 4.0 ng/ml, would be labeled abnormal. If all had a biopsy, potentially associated with hemorrhage and infection, 1.35 million or 75%, would undergo the procedure unnecessarily, meaning their PSA test indicated they had prostate cancer, when in fact they did not, which is referred to as a ‘false-positive.’27

The large difference between the 3% risk of death from prostate cancer vs. the 16% lifetime risk of being diagnosed with prostate cancer suggests many more cancers are diagnosed than are clinically important, supporting the concept of over diagnosis and over treatment.28 Very appropriately put, “The over diagnosis of prostate cancer reflects the fact that the cellular abnormality pathologists call prostate cancer is far too prevalent to be consistently important. How much prostate cancer is found seems to be directly related to how hard it is looked for.”27

Summary and Recommendations
The PSA level has served as an indication for a biopsy of the prostate and subsequent pathological determination of the presence or absence of histological grade of cancer. It has been noted that the interobserver variability among pathologists in a diagnosis of prostate cancer may be from approximately 55-75%.29 Treatments which follow for prostate cancer are associated with physical and psychological morbidities that exceed many other cancer treatments. Therefore, we cannot emphasize enough that the use of PSA as a disease marker is dangerous as it leads to overdiagnosis and overtreatment of men who would otherwise lead a relatively normal life. By putting so much emphasis on their absolute PSA number, men suffer from often unwarranted stress and anxiety, or “PSAdynia.”30 Overuse and misunderstanding of the utility of the PSA test has led to the creation of a new disease, “symptomless prostate cancer.”31

While we are not advocating the PSA test as presently utilized, for screening it is particularly important to note the proliferation of commercial PSA assays frequently yielding different results in the same individual. This is important to those individuals pursuing regularly scheduled PSA determinations relative to examining one’s PSA determinations in that they need to make certain their PSA determinations come ideally from the same laboratory or a laboratory using the same method and PSA calibration standard. Unfortunately, measuring PSA kinetics, other than at perhaps centers of excellence, is not as yet common practice in the medical community. The patient therefore may have to take the lead with his physician as to how he wants to proceed.

Prostate cancer is an age-related disease. The amount of prostate cancer you can find in men increases as they age and is related to how hard you want to look. Therefore, many cases of the detection of prostate cancer prompted by a PSA indicated biopsy have occurred serendipitously. Perhaps, the best way to view PSA is to place it within the context of the difference between a smoke alarm and a fire alarm. A smoke alarm indicates there is smoke, not necessarily fire and may direct attention to irregularities in the prostate, be they prostatitis, BPH or prostate cancer.

Promising studies have been looking at different isoforms of free PSA. These may have improved specificity for distinguishing BPH from prostate cancer, as well as for prostate cancer. Continued research on biomarkers is showing promise but thus far no putative markers have been validated as accurate, sensitive, and cancer-specific.

We all want a means to distinguish a non-aggressive (indolent) cancer from an aggressive prostatic cancer that kills, from most that do not. However, continuing with the current thinking “PSA testing is the best thing we have,” and continuing to use a test that cannot do what it has been purported to
do is not in keeping with the dictum *Primum non nocere* – “First do not harm.”

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reading by anyone that likes or hates me, and for those who have and have not heard of me, and anyone that is a man, woman, child or animal.

PPS. The Next Edition of my “Promoting Wellness for Prostate Cancer Patients” (Second Edition) Book should be available right now from Abbott Labs. It covers a quick overview of diet, supplements, and all forms of prostate cancer treatment. Talk to your support group leader or National Organization or health care provider (urologist…) about how to get a free copy.

126) Statin (cholesterol-lowering) drugs continue to get good news and should be offered to more healthy individuals.

Bottom Line: Statins given to healthy individuals may reduce the risk of dying from many causes (not just cardiovascular diseases). Maybe these drugs should be considered the real preventive daily multivitamin (so to speak).

I want you to think about this next paragraph in another way. Every time you see the word “statin” or “statins” pretend I am using the word “multivitamin” and I bet by the end of this section you will be very excited. There really are very few pills in the world that have proved themselves to be as powerful and as effective as these cholesterol-lowering agents. Personally, I believe they are one of the greatest anti-aging pills ever invented. Also, keep in mind that they are becoming very cheap, which is another important point. I went to my local pharmacy the other day and the price of pravastatin (Pravachol®) was only 10 dollars for a 6-month supply!!!! Wow! Anyhow, let’s get back to the good news...

Statins have received outstanding results from so many clinical trials that included individuals with heart disease that it was time to focus more attention on other areas where these medications might help folks. In other words, why not test healthy individuals on these medications because it might prevent a variety of problems later in life. One such past clinical trial from Japan found a benefit with low-dose statins (10 mg of pravastatin a day) for individuals with slightly elevated cholesterol that were otherwise healthy. Thus, the question also dangled out there of why not research statins on perfectly healthy individuals with normal LDL (bad cholesterol) and abnormal levels of an inflammatory marker known as hs-CRP (a controversial cheap risk marker) to see if some benefit can be derived?

This led to the design of one of the greatest prevention trials of my lifetime known as the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). The objective of this trial was to determine the impact of 20 mg daily of rosuvastatin (Crestor®) compared to placebo in healthy individuals over a 5-year time period. Healthy men (50 years or older) and women (60 years or older) with a LDL of less than 130 mg/dl and an hs-CRP level of 2.0 mg/l or greater were eligible. A total of 17,802 individuals from 1315 clinical sites in 26 countries were recruited for this randomized, double-blind, placebo-controlled, multi-center clinical trial to determine the impact of rosuvastatin on cardiovascular and other events. The average values at the beginning of the study were as follows: age was 66 years, 38% of the participants were female, LDL 108 mg/dl, hs-CRP 4.2 mg/l, HDL of 49 mg/dl, and triglycerides 119 mg/dl. Can you imagine this?! Before the drug was even given, again the average LDL or “bad cholesterol” level was 108 mg/dl!!! Very few individuals in the U.S. would be offered a statin with a number that good. So, cut to the chase Moyad and tell me what happened right now, please!

The trial was actually stopped after only 1.9 years because of the clear benefit derived from this statin drug!!! Let me repeat this amazing finding! The trial was stopped after 1.9 years because of the clear benefit from the statin drug compared to the placebo. The following conditions were all significantly REDUCED by the statin drug: heart attack was reduced by 54%, stroke by 48%, the need for a medical procedure by 23%, unstable chest pain by 47%, any cause of death by 20%, and cancer deaths by 20%!!!!!! (notice how I used 5 exclamation points to really emphasize my point…am I dramatic or what).

When the study ended the cholesterol values in the statin group were as follows (in other words, ask
yourself how close your numbers are to the following numbers that I am about to list:

- LDL 55 mg/dl,
- hs-CRP 1.8 mg/l,
- HDL of 55 mg/dl, and
- triglycerides 99 mg/dl.

Side effects were similar to the placebo. Rosuvastatin significantly reduced the risk of cardiovascular events and death. _______ (insert a swear word here or another word that demonstrates excitement and drama)!!! What can I really say here? Every single type of person also benefited in this trial (obese, thin, black, white, young, old, non-smokers, smokers, hypertensives, non-hypertensives, family history of heart disease, non-family history of heart disease...)! It is a shame that we have not looked more into statins for preventing other diseases. For example, one of the largest trials of men’s health also found that reduced levels of CRP could reduce the risk of erectile dysfunction. How about prostate cancer benefits?! Now, do you still really and truly believe that there is a better preventive pill than statins for completely healthy individuals?! For example, dietary supplements, like selenium or vitamin E, or even aspirin—well these do not have research as good as statins. If you do think there is a better pill than statins, there is swampland I must sell you in Michigan, authentic Big Foot photos I want to sell you, and finally, I was abducted by aliens as a baby and I will tell you what they told me, in private, about when the world is going to end for only 100 dollars per minute!

Some people ask me if everyone should go on a statin pill as they get older and I want to clarify that the answer is “no!” However, for people that are aggressive about their preventive health, which is not always a good thing, at least there is a pill that may help even the playing field so to speak. For example, I have a really bad family history and risk of everything that you can imagine (early cancer and heart disease deaths on both sides of my family and I am a walking melanoma risk) and that has always made me a little nervous, as you can imagine. So, I want to be aggressive with my preventive health and if I go down, I go down swinging till my last moment. So, what am I going to take regularly to reduce my risk (besides exercising 5-7 days a week, eating right, low stress, good mental health...) of dying young?? A multivitamin, vitamin E, selenium, lycopene,... give me a break! So, taking a statin may not be the best idea for everyone, but you have to figure out if it makes sense for you. There is always the concern of liver enzyme increases or muscle and joint pain, but again, everything has its risk to benefit ratio.

127) Belly fat in skinny or obese individuals can be a real problem.

Bottom Line: Belly fat is a major killer of skinny and obese people all over the world! Also, it is best to have a Body Mass Index (BMI) and waist circumference (WC) measurement (both of them) completed by your doctor at your next visit.

Stepping on a scale or using body mass index or BMI (kg in weight/meters squared in height, or lbs/inches squared multiplied by 704; where 25-29 is overweight and 30 or more is obese) measurements have been the standard for years to determine overall risk of dying young. However, belly fat measurements could correlate better than any other simple measurement in terms of cardiovascular, cancer and all-cause mortality, but this needed to be tested in a large prospective study. To determine the impact of excess belly fat in previously healthy men and women even in those with similar weight or BMI measurements a large study was recently completed. A total of 359,387 participants ages 25 to 70 years from 9 countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) study were followed in this prospective epidemiologic investigation. The mean follow-up was 9.7 years, and there were 14,723 participants that died. The lowest risk of death was for a BMI of around 25.3 for men and 24.3 for women. However, after adjusting for BMI, larger waist circumference (WC) measurements remained strongly correlated with all-cause mortality, but both measurements provided better correlation compared to one or the other. WC measurements that focus on abdominal fat tissue need to be used in addition to BMI.
(focuses on general fat) to predict the risk of dying young from all causes (cardiovascular, cancer, respiratory...). Both measurements offer synergistic value to individuals in predicting the risk of death from all causes, and need to be used.

“Apple shaped” body description implies that fat collects on the belly and “pear shaped” implies that your weight collects more around the hip or buttocks. This is one of the largest studies to demonstrate that being apple shaped, even if you are of a normal BMI, is unhealthy. The study also found that the BMI has value that WC does not, so both need to be utilized and measured in clinical practice. What makes this study powerful is that individuals were healthy at the onset and the researchers (not the study subjects) measured the participants to increase the accuracy of the results. Bottom line (pun intended) is that the whole world, even Europe, is becoming more obese, not just Americans, so people need to stop picking on us. Thus, even though they sell diet books that tell you that the French or Japanese or Chinese or Mediterranean populations do not get fat they are wrong! Obesity is becoming a global issue.

128) Vitamin E and/or selenium in high-doses does not prevent prostate cancer....ouch!!!

Bottom Line: There is no dietary supplement in high-doses that has yet to be found that definitely prevents prostate cancer, and I am not so sure these supplements do anything at all for cancer patients, except have the potential to make things worse. So there is no reason to take 400 IU of vitamin E or 200 mcg of selenium a day for "prostate health."

The Alpha-Tocopherol Beta-Carotene (ATBC) trial from Finland, published in 1998, demonstrated a reduction in prostate cancer incidence that was profound in men given 50 IU of vitamin E supplements daily compared to placebo. Another randomized trial published in 1996 found a large reduction in prostate cancer risk with 200 mcg of yeast-based selenium a day compared to placebo. These two randomized trials were the background for initiating the largest prevention trial in prostate cancer his-

tory known as “SELECT.” This trial was initiated to determine the impact of 400 IU of synthetic vitamin E daily, 200 mcg of selenium daily or the combination on the incidence of prostate cancer. A total of 35,533 men from 427 clinical sites in North America and Puerto Rico were assigned to one of 4 groups (Vitamin E, Selenium, both agents or placebo) for a planned minimum follow-up of 7 years and a maximum of 12 years. Men had to be 50 years or older if African-American, and 55 years or older otherwise with a PSA level of 4 ng/ml or less, and a negative digital rectal exam (DRE). Median follow-up was 5.5 years, and vitamin E, selenium, nor the combination demonstrated a reduction in prostate cancer or any other cancer, so the trial was stopped early. There was an almost significant (p=0.06) increased risk of prostate cancer in the vitamin E group, and an increased risk of type 2 diabetes in the selenium group (p=0.16). There was no increased or decreased risk of a serious side effect when taking the combination of vitamin E and selenium. Vitamin E or selenium, alone or together does not prevent prostate cancer in healthy men.

Wow! I am going to get in trouble for being candid, but the SELECT trial cost 125 or so million dollars of tax-payer money! Now, there is not much to show for it except to be politically correct, and state that at least researchers should learn a lot from this trial about prostate cancer and other disease risk with further follow-up. This is the so called “glass is 10% full approach.” Should this trial have ever been allowed to commence? Probably not, but forget about my opinion for a second. How about the fact that these supplements never really had clear evidence that they even promoted heart health, or prostate health in healthy non-smoking men?!

The most important point to remember about this trial is that 1 man died of prostate cancer, but there were about 500 deaths from cardiovascular disease during the trial and it was the number one cause of death in the vitamin E group, selenium group, combination group, and placebo group! Do I really need to say anything more?! (In other words, take care of your heart health as much as possible whether or not you have been diagnosed or treated for prostate cancer, because the lifestyle changes
that help your heart are the only ones thus far that may help your prostate...either way in this situation you increase your odds the most of doing better).

129) High-doses of vitamin E every other day and high-dose vitamin C does not prevent prostate cancer...ouch again!!!
(Reference: Gaziano JM, et al., JAMA 301:52-62, 2009)

Bottom Line: 400 IU of vitamin E every other day or 500 mg of vitamin C daily does not reduce the risk of prostate cancer.

Vitamin E and vitamin C in higher doses had some evidence that they may reduce the risk of cancer. Some of the same researchers that worked on the Physicians’ Health Study I which showed aspirin every other day could reduce the risk of a heart attack decided to see if any of these dietary supplements could reduce the risk of cancer. The clinical trial was to determine the impact of a high dose of vitamin E or vitamin C on the risk of prostate and total cancers.

A total of 14,641 male physicians in the U.S. age 50 years or older were enrolled, and most men were healthy and without a history of cancer. Men were randomized to 400 IU every other day of synthetic vitamin E and/or 500 mg daily of vitamin C. There was also a separate group of men taking a multivitamin daily compared to a placebo.

The mean follow-up was 8.0 years, and there were approximately 1000 confirmed prostate cancer cases and almost 200 other cancers. Vitamin E or C had NO impact on prostate or any other cancer. A larger number of hemorrhagic strokes (bleeding into the brain basically) occurred in the vitamin E group compared to placebo (HR=1.74, 39 cases compared to 23). There was also a group of doctors that were taking a Centrum Silver multivitamin daily, but this multivitamin group has not yet been analyzed and is still continuing to take the supplement compared to the placebo, so these results will be available in the next few years.

Vitamin E or vitamin C supplementation did not reduce the risk of prostate or any other cancer. Keep in mind that this is basically the same group of doctors that we reviewed in a previous issue that were found to increase their chances significantly of reaching the age of 90 years or more if they followed a multitude of heart healthy lifestyle factors such as not being obese, not smoking, and exercising almost daily. What irony! In other words, can longevity be found in greater probability with lifestyle changes compared to an over the counter pill (remember statins are not over the counter yet in the U.S., which is when I will change this statement)!! Yes, but you’re not going to see that in a commercial on television because it's just boring and doesn't make any big time bucks! I think it is time to ask for some of that bail out money from Washington D.C., especially for vitamin E manufacturers, because high-dose vitamin E has been a big disappointment. Vitamin C supplements still look interesting in some other areas (colds, helping iron absorption...), but in the area of prostate cancer prevention it has not been looking good.

130) Androgen Deprivation Therapy (ADT) does not appear to increase the risk of cardiovascular deaths in men with locally advanced prostate cancer (regardless of what some others may be saying).

Bottom Line: Side effects of ADT require close monitoring for sure, but the apparent risk of cardiovascular death with these drugs may have been overestimated.

ADT, especially LHRH agonists have been around for over 20 years, and the issue is no longer whether or not they reduce the risk of death from prostate cancer (they obviously do). The current issue is the potential side effects, some minor and some major, that may occur with long-term use of these products. The largest concern has to be whether or not ADT increases the risk of cardiovascular deaths or mortality. To determine whether or not ADT increases cardiovascular mortality, some researchers analyzed retrospectively the risk of mortality from cardiovascular causes from the randomized trial RTOG 92-02. This trial primarily compared the impact of short (4 months) versus long-term (28 months) ADT in men with locally advanced prostate cancer receiving radiation treatment.
Median age was 70 years and follow-up was approximately 8.1 years and 185 cardiovascular deaths occurred during the trial, and 765 total deaths (24%) occurred out of a total of 1554 men that began the trial. At 5-years there was no significant difference in cardiovascular deaths between long (5.9%) and short-term (4.8%) ADT arms. Age, diabetes, or a previous history of cardiovascular disease were better predictors of cardiovascular mortality, but the amount of time on ADT (duration) was not associated with cardiovascular mortality regardless of how the definition of heart disease was perceived. So, ADT may not increase the risk of cardiovascular death in men with locally advanced prostate cancer.

Significantly more patients in the long-term ADT arm (30%) began the trial with a history of cardiovascular disease compared to the short-term arm (25%, p=0.03), but there was still no difference in cardiac deaths with ADT. In addition, all randomized trials or prospective studies completed thus far have currently been unable to find a significant or consistent increased risk of cardiovascular mortality with ADT. However, it is true that ADT may cause weight gain, glucose changes and possibly triglyceride increases, so this may increase the risk of metabolic syndrome and heart disease, especially in a high-risk cardiac patient.

Regardless, as long as cardiovascular disease is the number 1 cause of death in men with and without prostate cancer, I have always believed that men treated for localized or locally advanced prostate cancer need to do whatever is needed to reduce their risk of cardiovascular disease and death to as close to zero as possible. THAT IS THE REALLY BOTTOM LINE!

131) Weightlifting and/or aerobic exercise reduces fatigue after radiation treatment for prostate cancer.
(Reference: Segal RJ, et al., Journal of Clinical Oncology, published on-line early because the study findings were so important, 2008)

Bottom Line: Weightlifting improves or maintains multiple health parameters such as quality of life, lipids (cholesterol), muscle mass, and strength.

Previous studies found that weightlifting about 3 times a week reduced fatigue from androgen deprivation therapy (ADT) and improved quality of life in patients with advanced prostate cancer. Men with more localized or locally advanced tumors had not been evaluated adequately using a similar protocol to determine if side effects could be reduced in this group. Researchers determined the impact of aerobic exercise compared to weightlifting in men receiving radiation therapy for prostate cancer.

A total of 121 participants were placed in one of 3 groups for 24 weeks: usual care (n=41), aerobic exercise (n=40), or weightlifting (41). The exercise groups were asked to commit 3 days a week for approximately 45 minutes per session. This randomized controlled trial included patients receiving radiation therapy with and without ADT. The primary endpoint was fatigue, as measured by the validated Functional Assessment of Cancer Therapy (FACT-F) scale.

There was an 85% adherence to the protocol (this is really good and means most people stuck with the program), and approximately 60% of participants in each group were on ADT. Aerobic exercise and weightlifting both significantly (p=0.01, p=0.004) reduced fatigue over the short-term (12-weeks), but weightlifting had more significant (p=0.002) long-term effects on this endpoint. All of the following were significantly improved with weightlifting compared to usual care: quality of life, fitness, lower and upper-body strength, triglycerides, and maintaining (not increasing) body fat. PSA, testosterone, and hemoglobin did not improve significantly with aerobic or resistance (weightlifting) exercise. So, now it is clear, aerobic and resistance exercise should be encouraged in men undergoing radiation therapy and/or LHRH treatment for cancer (with the approval of the oncologist).

THAT IS ALL FOLKS! See you in the Spring where we can talk about new prostate cancer discoveries, more fun diet and nutritional supplement stuff, and who else is going to get the government bail-out money cause I know darn well we aren’t going to get any! How about throwing some of that money toward cancer research?! I got my fingers crossed
that Michigan Football will have a good recruiting class, and that President Obama is going to increase research funding, and that the Provenge vaccine will work so that patients can get it in 2009! Man, I hope I'm right!

INNOVATIVE THERAPIES IN PROSTATE CANCER
By E. Roy Berger, MD, FACP
East Setauket, NY
Email: erbmd@yahoo.com
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INTRODUCTION
It is estimated that more than 28,000 American men will die this year because of prostate cancer. Most of these men will have reached the advanced stages of hormone refractory prostate cancer where their treatment options are limited. For these men, no FDA-approved, second-line treatment options are available once docetaxel has failed. Fortunately, there are numerous innovative therapies in development. As oncologists, it is important that we be aware of these treatment options. This review provides an overview of these innovative therapies.

IMMUNOTHERAPY
There are currently two treatment modalities in development that use the body’s own immune system to fight prostate cancer: 1) sipuleucel-T immunotherapy and 2) vaccine immunotherapy.

Sipuleucel-T immunotherapy. Sipuleucel-T is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen-presenting cells that have been activated in vitro by means of a recombinant fusion protein. The recombinant fusion protein, PA2024, is composed of prostatic acid phosphatase (PAP) linked to granulocyte–macrophage colony-stimulating factor (GM-CSF), an immune cell activator. Using this method, PAP serves as the antigenic moiety while the GM-CSF portion targets the fusion protein to cells expressing the GM-CSF receptor and facilitates internalization and processing of the PAP antigen.

A pivotal double-blind multicenter phase III study (D9901) by Small and colleagues² randomized 127 asymptomatic, metastatic, androgen-independent patients with prostate cancer to receive sipuleucel-T (n = 82) or placebo (n = 45), given as infusions in weeks 0, 2, and 4. The placebo group was treated with peripheral blood monocytes that had not been exposed to antigen.

The results of this study were very promising. There was a 31% reduction in the time to disease progression in the sipuleucel-T arm relative to the placebo arm. The median time to disease progression in the treatment and control arms was 11.7 and 10.0 months, respectively. In addition, there was a 41% reduction in the risk of death in the sipuleucel-T arm compared with placebo, with a median survival benefit of 4.5 months (25.9 mo vs. 21.4 mo). At 36 months, 34% of the group treated with sipuleucel-T was alive compared with only 11% of the control group.

A second study, D9902A, was identical in design to D9901. Enrollment was halted at 98 patients based on a subset analysis of D9901, and a trend in the same direction as D9901 was observed.³ In an integrated analysis of both studies, the total number of patients was 225 and both P-values and hazard ratios showed improvement in median survival (23.2 mo, sipuleucel-T group; 18.9 mo, placebo group). At 36 months, 33% of the sipuleucel-T treated group was alive versus 15%, of the placebo group. Toxicity caused by sipuleucel-T therapy was minimal, primarily a flu-like syndrome during and after infusion.³

At present, the FDA has given sipuleucel-T an ‘approval’ letter that is dependent on an interim or final analysis of results from the IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment, also known as D9902B) trial, a randomized controlled study involving 512 patients. In early October, researchers released an interim analysis of IMPACT. The independent data monitoring committee (IDMC) reported a 20% reduction in the risk of death in the sipuleucel-T arm compared with placebo (hazard ratio, 0.80; 95% confidence interval, 0.610-1.051). The analysis also found that the treatment effect observed at 24 months’ follow-up was consistent with an integrated analysis of findings from previous phase III trials in this patient population at 24 months. Observing no safety concerns, the IDMC recommended that the IMPACT study proceed to its final analysis. The FDA will await results of this final analysis before granting approval to sipuleucel-T.

Vaccine immunotherapy. Cell Genesys Inc has developed an immunotherapy paradigm designed to stimulate a patient’s immune system to fight cancer effectively. This immunotherapy uses tumor cells that are genetically modified to secrete GM-CSF. It is speculated that the antitumor immune response that occurs throughout
the body may result in the destruction of tumor cells that persist or recur following surgery, radiation therapy, or chemotherapy treatment.

Cell Genesys immunotherapy uses multiple intradermal injections of cryopreserved prostate cancer cell lines (CG1940 + CG8711) that have been irradiated after being transfected with GM-CSF. The injections are administered biweekly or every 3 weeks for 6 months, followed by monthly injections for life.

Data from two phase II trials show promise. In the first trial, 34 patients with hormone-refractory prostate cancer received either a low dose (n = 24) or a high dose (n = 10) of the immunotherapy as their only cancer therapy for up to 6 months. The combined median survival for both dose groups was 26.2 months.\(^4\)

The second phase II trial enrolled 80 patients with hormone-refractory prostate cancer. In 22 patients who received the higher dose, the median survival has not yet been reached but is expected to meet or exceed 29.1 months based on the patients still in follow-up.\(^4\)

Based on these results, two phase III studies have begun that involve patients with metastatic hormone-refractory prostate cancer.\(^4\) In the first trial, the safety and efficacy of CG1940 + CG8711 immunotherapy is being compared with docetaxel plus prednisone. In the second trial, the safety and efficacy of CG1940 + CG8711 immunotherapy plus docetaxel is being compared with docetaxel plus prednisone. Recent issues of safety and likely lack of survival benefit have stopped accrual to these trials.

**CAN WE IMPROVE UPON TAX327?**

The landmark TAX327 study by Tannock and colleagues\(^5\) showed docetaxel to be the only medication to improve survival in hormone-refractory prostate cancer. Accompanying that study, the SWOG 9916 study by Petrylak and colleagues\(^6\) added estramustine to docetaxel and observed a 2-month improvement in survival (compared with a mitoxantrone + prednisone arm), but this was offset by an increase in adverse events, especially thromboembolic and hypercoagulable events. This latter study best exemplifies the problems that have faced many researchers in trying to improve the efficacy of docetaxel therapy without compromising safety. The following are a few combination therapies under investigation that will hopefully improve efficacy and safety.

**Sipuleucel-T followed by docetaxel.** Data presented by Dr. Petrylak at the Chemotherapy Symposium Foundation in November 2006 looked at potential synergies between immunotherapy and chemotherapy.\(^7\) Exploratory analyses of the integrated D9901/D9902A data assessed the influence of sipuleucel-T immunotherapy in patients who received docetaxel chemotherapy after sipuleucel-T as their primary treatment.

The researchers observed that patients initially given sipuleucel-T followed by docetaxel after progression had the longest survival time (34.5 mo) compared with patients who initially received placebo followed by sipuleucel-T followed by docetaxel (25.7 mo) or patients who only received docetaxel after placebo (20.2 mo). While better-designed studies are needed to confirm these results, this study is promising and possibly opens up a whole new field with the use of immunotherapy in the treatment of prostate cancer.

**Docetaxel plus calcitriol.** Preclinical studies have shown that calcitriol, an oral form of vitamin D, enhances cell death in several prostate cancer cell lines. To that end, a highly concentrated formulation of calcitriol was developed for use in cancer trials. Preliminary data from the phase III ASCENT (Androgen Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere) trial was promising,\(^8\) but this trial was recently terminated based on a higher death rate observed in the treatment arm. At present, no further studies are in development.

**Docetaxel plus vinorelbine.** Vinorelbine is a microtubulin inhibitor that affects polymerization of the microtubules. In a phase II study conducted by Goodin and colleagues,\(^9\) 40 patients with progressive metastatic disease were given docetaxel (69 mg/m\(^2\) on day 1) plus vinorelbine (15 mg/m\(^2\) on days 1 and 8 of a 21-day cycle. The study observed a decrease in prostate-specific antigen (PSA) >50% in 19 patients (37%) with no prior chemotherapy, and in 21 patients (29%) who had received one or more prior chemotherapy treatments. These results are encouraging but currently no known phase III trials for this combination are underway.

**Docetaxel plus capecitabine.** Capecitabine is an oral thymidine synthetase inhibitor. A phase II trial by Ferrero and colleagues\(^10\) studied the efficacy and safety of docetaxel (35 g/m\(^2\)/wk for 3 wk) plus capecitabine (625 mg/m\(^2\) twice daily [days 5-18] every 28 days for 4 cycles) in 46 patients with hormone-refractory prostate cancer. The researchers observed that 68% of the patients achieved a biological response and 32% normalized their PSA value. The median overall survival time was 17.7 months while the main grade 3 to 4 toxicities were cuta-
neous toxicity (13.1%) and changes in nails (6.5%). More studies with this combination in patients with advanced prostate cancer are in development.

**Docetaxel plus thalidomide.** Thalidomide is believed to have an immunomodulatory effect on the tumor microenvironment, but its mechanism of action is poorly understood. In a randomized phase II study performed by Dahut and colleagues, 75 patients with androgen-independent prostate cancer received either thalidomide (200 mg/day) plus docetaxel (30 mg/m²/wk for 3 wk) or docetaxel alone. The response rates were 53% for the combination therapy and 37% for the docetaxel alone group. The median progression-free survival (PFS) was 5.9 months for the combination therapy and 3.7 months for docetaxel alone. Toxicities in both groups were manageable after administration of prophylactic low-molecular-weight heparin.

This combination may also be enhanced by the addition of bevacizumab. At this year’s ASCO meeting, Ning and colleagues reported the combination of bevacizumab (15 mg/kg/day for 21-day cycles), thalidomide (200 mg/day), and docetaxel (75 mg/m²) in patients with metastatic castration refractory cancer (N = 60) resulted in 88% of the patients showing a decline in PSA >50% and an estimated median PFS of 18.2 months. The combination was well tolerated, and more studies are warranted.

**OTHER NOVEL TREATMENT OPTIONS**

**Abiraterone.** Abiraterone acetate is an irreversible inhibitor of CYP17 that decreases testosterone to undetectable levels. At this year’s ASCO meeting, Danila and colleagues reported on the preliminary results of a phase II trial in patients with advanced castrate-resistant prostate cancer who were given oral abiraterone acetate alone (1,000 mg daily for 28-day cycles) or in combination with prednisone (5 mg). The addition of prednisone was to reduce adverse events. Preliminary results from 38 patients showed that 44.7% (17/38) of patients had a decline in PSA >50% and nonprogression of disease was observed in 9 patients after 6 months.

In a recent phase I study by Attard and colleagues, 21 men with hormone-resistant prostate cancer were given once-daily, continuous abiraterone acetate (250 to 2,000 mg). They observed declines in PSA ≥30%, 50%, and 90% in 14 (66%), 12 (57%), and 6 (29%) patients, respectively. Furthermore, the medication was well tolerated and the anticipated toxicities attributable to a syndrome of secondary mineralocorticoid excess (i.e., hypertension, hypokalemia, and lower-limb edema) were managed with a mineralocorticoid receptor antagonist.

More phase II trials and a phase III trial are expected to begin shortly.

**Atrasentan.** Atrasentan is an oral selective endothelin-A receptor antagonist that may inhibit cell proliferation and interfere with angiogenesis. In 2007, Nelson and colleagues reported on a phase III trial involving 467 patients with nonmetastatic hormone-refractory prostate cancer randomized to receive atrasentan (10 mg) and 474 patients randomized to receive placebo daily. At the end of the study, no statistically significant differences in efficacy were observed. At present, the testing of atrasentan in future clinical trials is being re-evaluated.

**Satraplatin plus prednisone.** Satraplatin is a platinum chemotherapeutic agent under development for several cancer types, including hormone-refractory prostate cancer. The phase III SPARC (Satraplatin and Prednisone Against Refractory Cancer) trial randomized satraplatin (80 mg/m² on days 1–5 every 5 wk) plus prednisone (5 mg twice daily) to prednisone alone. Preliminary results of the study were presented at this year’s ASCO meeting by Sartor and colleagues, who reported that the combination of satraplatin plus prednisone was associated with statistically significant improvements in PFS, time to progression, PSA response, objective tumor response, pain response, and duration of pain response. Surprisingly, overall survival was similar in the two groups (satraplatin + prednisone, 61.3 wk; prednisone alone, 61.4 wk). The treatments were well tolerated. There was no survival benefit, however, so this compound will not be pursued.

**Sorafenib.** Sorafenib blocks the enzyme RAF kinase, which helps regulate signaling pathways involved with cell division and proliferation. It also blocks tumor angiogenesis. At this year’s ASCO meeting, Aragon-Ching and colleagues provided an updated analysis of a phase II study involving 24 patients with metastatic castrate-resistant prostate cancer given sorafenib (400 mg twice daily in 28-day cycles). Unfortunately, the study concluded that sorafenib has only a modest activity as a second-line treatment and was not well tolerated by many of the patients.

Slightly better results were obtained in a phase II study that combined sorafenib (400 mg twice daily) with bicalutamide (50 mg/day in a 28-day cycle) in 20 patients with hormone-refractory prostate cancer. Preliminary results of the study by Beardsley and colleagues showed this combination to be fairly well tolerated and, to date, 6 of the 20 patients have a confirmed PSA response. This trial is proceeding to the second stage of the study.
Romidepsin (FK228). Romidepsin is a bicyclic depsipeptide that inhibits histone deacetylase, which results in alterations in gene expression and the induction of cell differentiation, cell-cycle arrest, and apoptosis. Parker and colleagues reported results of a phase II trial involving the use of romidepsin (13 mg/m² on days 1, 8, and 15 of a 28-day cycle) in patients with hormone-refractory prostate cancer (N = 31). The study concluded that treatment with romidepsin is associated with a disease control rate of 14% and a PSA response rate of 7%. Constitutional toxicities were prominent, but no grade 4 events were observed. The authors concluded that studies of romidepsin in combination with other active agents are warranted.

MDV3100. MDV3100 is a new antiandrogen with a high affinity for the androgen receptor. While clinical results with this drug are still in the early stages, the results of a phase I trial presented at this year’s ASCO meeting by Scher and colleagues showed that MDV3100 had a dose-response effect on reducing PSA levels. Furthermore, it appears to perform well in castrate-resistant patients who are chemo-naïve (55% had a 50% decline in PSA) or who have previously been given docetaxel (42% had a 50% decline in PSA).

CONCLUSIONS
Although there have been a number of negative studies, the above data lend a sense of excitement for the future of treatment of men with prostate cancer. The clinical research may lag far behind that for some other tumors, such as breast cancer, but there is reason for optimism since survival differences are now being seen in a patient population that has never before benefited from any form of therapy.

ABOUT THE AUTHOR:
Affiliation:
Dr. Berger is currently an independent consultant, formerly with the North Shore Prostate Cancer Consultation & Treatment Service and North Shore Hematology Oncology Associates in East Setauket, NY.

Address all correspondence to:
Email: erbmd@yahoo.com
If you are unable to reach Dr. Berger by Email, please contact PAACT at 616-453-1477.

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Memorial Contributions

In Loving Memory of Lloyd J Ney, Sr.
Founder of PAACT, INC., Grand Rapids, MI

Mary & Robert Jenkins
James C Goodwin
Robert L Kroner
Roland Guerin
Frank Wuerfel
Leopold Grill
Guy Willson
Donna Stark

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Sidney & Anita Blank
Jimmy Jack Beale
Donald Campbell
Mike Bohannon
Conway Taylor
Val Hoffman

Dr. & Mrs. Eugene P Smith
Fay & Seymour Zayon
May & Vincent Ting
Jeff & Mary Moore
John Apostolidis
John B Cataldo
John E Drake

In Recognition of Lloyd Ney's 10 Year Anniversary Since His Passing

Dr. Fred Lee, Sr.

For years you’ve been asked to buy into all that health advice out there—to buy the books, the machines, the newsletters, the pills, the injections, and the surgeries.

Now it’s time to put all those things aside and empower yourself with the knowledge to sort through all the BS health advice (that’s Bogus Science, of course!) to find a truly stronger, healthier you.

Taking a common sense and often-lighthearted approach to the research and myriad of health information out there, Dr. Mark Moyad pulls back the curtain on many half-truths and misinformation and helps you develop a plan to improve your overall health and wellness.

Please send me _______ copies of Dr. Moyad’s No BS Diet Health Advice at $19.95 each plus shipping, $5.00 shipping on first copy (US destinations), $7.50 on first copy to Canada; $3 each for additional copies.

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<table>
<thead>
<tr>
<th>In Loving Memory of James Cotter</th>
</tr>
</thead>
<tbody>
<tr>
<td>His Mother, Sophia Cotter</td>
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<tr>
<td>North Reading Middle School Staff</td>
</tr>
<tr>
<td>Matthew &amp; Mary Maguire</td>
</tr>
<tr>
<td>Charles &amp; Elaine Mahaffy</td>
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<tr>
<td>Nancy Cali &amp; James Lutz</td>
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<td>Ken &amp; Marie Maxim</td>
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<tr>
<td>John &amp; Sally Glouse</td>
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<tr>
<td>Lisa Staskowski</td>
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<tr>
<td>Doris Harriman</td>
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<tr>
<td>Megan Upercraft</td>
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<tr>
<td>Thea Wheeler</td>
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<tr>
<td>Donna Barady</td>
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<tr>
<td>Adrienne Figus &amp; Mike Zombek</td>
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<tr>
<td>Jim &amp; Pam Rogers &amp; Family</td>
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<tr>
<td>Richard &amp; Elizabeth Bedient</td>
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<tr>
<td>Roger, Terry &amp; Matt Tanner</td>
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<td>Katelyn Upercraft</td>
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<td>Liska Savage</td>
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<td>Thomas Bell</td>
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<td>His Sister Barbara Cotter &amp; Tim Walsh</td>
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<td>Deansboro Library Book Club</td>
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<td>Susan Hodge &amp; Alan Braverman</td>
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<td>William &amp; Barbara Ambs</td>
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<td>David &amp; Dana O'Brien</td>
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<td>Lucy Savage</td>
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<td>Ann P Allen</td>
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<td>Dan Cowen</td>
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<th>In Loving Memory of Jason Adleman</th>
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<td>Jacqueline Maarse</td>
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<td>Ken &amp; Lori Greene &amp; Family</td>
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<tr>
<td>Courtney Williams</td>
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<tr>
<td>Anonymous</td>
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<tr>
<td>Edward Kucera</td>
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<tr>
<td>Carol A Arnold</td>
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<thead>
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<th>In Loving Memory of William R Nielson</th>
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<td>Helen D Nielsen</td>
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<td>Mary Lamielle</td>
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<td>H Michael &amp; Phyllis Weitzman</td>
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<th>In Loving Memory of Thomas Lubnau, Sr.</th>
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<tbody>
<tr>
<td>Jeremy D Michaels</td>
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<tr>
<td>Ennis Wuite</td>
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<td>Jimmy Jack Beale</td>
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<th>In Loving Memory of Harris Baum</th>
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<td>Elyse Fuhr</td>
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<td>Sue Goldman &amp; Jim Calafiore</td>
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<th>In Loving Memory of Burton Weiss</th>
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<tr>
<td>Dorothy Weiss</td>
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<th>In Loving Memory of Ed Marges, Sr. &amp; Jack Beeler</th>
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<td>Edward &amp; Dawn Marges</td>
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<th>In Loving Memory of My Brother, Pat</th>
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<td>Michael P Springer, Jr.</td>
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<th>In Loving Memory of Dan November</th>
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<tr>
<td>Vivian November</td>
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<th>In Honor of Dr. Stephen Anderson's Birthday</th>
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<tbody>
<tr>
<td>Henry P Anderson</td>
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</tbody>
</table>

20 Prostate Cancer Communication / March 2009
## Contributions ($1,000 and Above)

Albrecht, Ted  
Beale, Jimmy Jack  
Causey, Charles  
Rizzi, Ben  

## Contributions ($500 to $999)

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Hoagland, Jim  
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Hone, John  
Hopkins, Robert  
Hoy, Tom  
Janek, George  
Jensen, Eric  
Johnson, Donald  
Johnson, Walter  
Kadan, William  
Kahn, Morley  
Kevin, Herbert  
Kivitz, Seymour  
Kortebein, Stu  
Krejci, John  
Kusnirik, Robert  
La Croix, Ray  
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Lewis, Deward
Link, Bernard  
Livensparger, Karl  
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Mahr, Ray  
Maki, Curtis  
Maples, R Wayne  
Marcario, Michael  
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Marston, John  
Martin, Bill  
Martin, Donald  
Martin, Leo  
Martin, Troy  
Martinez, Dennis  
Mason, Charles  
Meetze, William  
Mendelsohn, King  
Monchil, Donald  
Monnig, Hugo  
Moore, Booker  
Moore, T Edwin  
Morrison, James  
Myers, Pieter  
Nathanson, Benjamin  
Neuner, Billie  
Nichols, Bernie  
Nickles, John  
Nystrom, Donald  
Ott, David  
Panfil, John  
Parker, Maelyn  
Parr, Mike  
Pasciak, Eugene  
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Perless, Leonard  
Perry, Edgar  
Peterson, William  
Pfadenhauer, Paul  
Phillips, Caroline  
Pierson, Glen  
Pilotto, Louis  
Pintar, Harold  
Purdy, Peter  
Rawls, John  
Richardson, Charles  
Robinson, Elliott  
Roedl, Douglas  
Rohrer, Dan  
Roth, Herman  
Rowe, Robert  
Royall, Kenneth  
Savino, Joseph  
Scalfani, John  
Schafer, Hal  
Scharf, Leonard  
Schlaug, Robert  
Schumacher, Paul  
Scotford, Al  
Sellers, William  
Senko, Peter  
Sher, Harold  
Shoesmith, John  
Shulman, Herbert  
Silvers, Bill  
Slakter, Malcolm  
Smith, Thomas  
Steinfeld, Richard  
Stellhorn, Theodore  
Stern, Henry  
Stern, Robert  
Steward, Philip  
Stone, Lawrence  
Stone, Robert  
Suhr, James  
Sullivan, James  
Szarko, Walter  
Taormina, Sam  
Tehan, George  
Templeman, John  
Thompson, C Thomas  
Thompson, Walter  
Thorn, Bruce  
Van Howe, Ken  
Vinciguerra, Art  
Wagner, Jerry  
Warfield, John  
Weir, Robert  
Weldon, John  
Western, James  
Wikstrom, Robert  
Willis, J Bixby  
Wilson, William  
Wojnar, Edward  
Wolfe, Stuart  
Wright, James  
Wright, Lacy  
Yeager, Gresham  
Yunn, Bill  
Zbovoyvsky, James  
Zeiders, Steven  
Zimmerman, Alfred  
Hong, Robert  
Honymar, Richard  
Hostetler, Connie  
Jackiewicz, William  
Jacobson, Jerome  
Jansky, Louis  
Jenkins, R.G.  
Jennings, Chuck  
Kanor, Steven  
Kapso, Howard  
Kelly, Charles  
Kerns, Cordon  
Knobloch, John  
Kobliner, Harold  
Kuhn, Edwin  
Largman, Ted  
Lederle, Donald  
Leve, Marilyn  
Lewis, Ellwood  
Logrippo, Frank  
Long, Derek  
Luna, Linda  
Lupo, Carmen James  
Madison, R Peter  
Martis, Kenneth  
Mazurek, Robert  
McCann, Alfred  
McCarthy, Michael  
McDowell, H Clay  
Mezhinsky, Victor  
Middleton, Byron  
Miller, Donald  
Mills, Norman  
Mirza, Zareen Taj  
Nachtigal, John  
Nagel, Thomas  
Napier, Evan  
Narchi, Joseph  
Nathan, Stephen  
Nathan, William  
Niedermaier, George  
Nordling, Carl  
Norberg, Richard  
Normandeau, Michael  
Novick, John  
Nunn, Roger  
Nystrom, Donald  
Oakey, James  
Oakes, Raymond  
Palkowski, Ronald  
Panetta, Ralph  
Parsons, Robert  
Pekelney, Albert  
Pence, Mayford  
Perry, Herbert  
Peterson, Peter  
Pinkard, Dennis  
Plotkin, Nathan  
Ripps, Wilbur  
Schroeder, Alfred  
Secor, Robert  
Secrist, C Robert  
Sietert, William  
Siersdorfer, John  
Solazzo, Dominic  
Solomonson, Gordon  
Sommer, Curt  
Sonder, Edward  
Starr, Robert  
Stevick, Donald  
Stuart, William  
Taub, Elston  
Townsend, Andy  
Trundle, James  
Whitney, Robert  
Williams, James  
Wilson, Bill  
Wilson, F.W.  
Woolhouse, Robert  
Ziemke, Donald

**Miscellaneous Contributions (less than $50)**

Abt, William  
Agresti, Louis  
Amendt, Kenneth  
Andrus, Dean  
Anonymous  
Baker, Eugene  
Beer, Harry  
Bieber, Milton  
Breen, Dermott  
Buck, Sydney  
Burton, D Jeff  
Busch, Edward  
Cain, Louis  
Campione, Jim  
Cheng, Chi  
Cunningham, Patrick  
Dardzinski, Donald  
Dick, Ron  
Echols, Gene  
Edie, Charles  
Edwards, Morris  
Eisenberg, Albert  
Eldridge, David  
Estell, Robert  
Filippello, Vincent  
Fowler, Vernon  
Gettleman, Marvin  
Gewertz, Albert  
Givone, William  
Glover, Vern  
Goodale, George  
Gordon, Charles  
Gordon, Neuman  
Haick, Robert  
Hammar, Fred  
Hargrave, Irv  
Harvey, Andrew  
Heinke, Wayne  
Henderson, Willard

**Contributions by State & Province**

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22 **Prostate Cancer Communication** / March 2009
### FINANCIAL SUMMARY REPORT

*(January 1, 2008 through December 31, 2008)*

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<th>General Fund</th>
<th>Value</th>
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<td>Membership Contributions</td>
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<tr>
<td>Memorial Income</td>
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<td>Trusts &amp; Bequests</td>
<td>11,875.00</td>
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<td>Investment Income</td>
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<td>Reimbursed Expenses</td>
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<td><strong>Total Revenues</strong></td>
<td>166,402.64</td>
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<tr>
<td><strong>Total Balance on Hand and Revenues</strong></td>
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<td><strong>EXPENDITURES</strong></td>
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<td>Employee Wages</td>
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<td>Payroll Taxes</td>
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<td>Insurance (Health, House, Workman’s Compensation)</td>
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<td>Outside Services, Labor</td>
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</tr>
<tr>
<td>Rent</td>
<td>15,000.00</td>
</tr>
<tr>
<td>Meals, Motel, and Transportation</td>
<td>4,338.41</td>
</tr>
<tr>
<td>Auto Expense</td>
<td>3,785.91</td>
</tr>
<tr>
<td>Printing</td>
<td>25,759.17</td>
</tr>
<tr>
<td>Postage and Delivery</td>
<td>23,869.80</td>
</tr>
<tr>
<td>Telephone</td>
<td>2,797.91</td>
</tr>
<tr>
<td>Service Fees/Licenses &amp; Permits</td>
<td>3,496.92</td>
</tr>
<tr>
<td>Program Expense-Conference Exhibit Fees</td>
<td>0.00</td>
</tr>
<tr>
<td>Office and Computer Supplies</td>
<td>4,612.35</td>
</tr>
<tr>
<td>Utilities - Refuse</td>
<td>76.00</td>
</tr>
<tr>
<td>Repairs (Building, Equipment)</td>
<td>193.74</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1,747.46</td>
</tr>
<tr>
<td><strong>Total Expenditures</strong></td>
<td>213,006.11</td>
</tr>
<tr>
<td>Balance on Hand December 31, 2008</td>
<td>1,463,691.13</td>
</tr>
<tr>
<td><strong>Assets</strong></td>
<td></td>
</tr>
<tr>
<td>Checking Account</td>
<td>22,281.31</td>
</tr>
<tr>
<td>Petty Cash</td>
<td>50.00</td>
</tr>
<tr>
<td>Savings Account</td>
<td>29.63</td>
</tr>
<tr>
<td>Certificates of Deposit, Stocks, and Bonds</td>
<td>932,652.68</td>
</tr>
<tr>
<td>Money Market Funds</td>
<td>162,410.67</td>
</tr>
<tr>
<td>Equipment</td>
<td>15,705.17</td>
</tr>
<tr>
<td><strong>Net Assets</strong></td>
<td>1,133,129.46</td>
</tr>
<tr>
<td><strong>Foundation Fund Balance</strong></td>
<td>323,151.40</td>
</tr>
</tbody>
</table>
### PAACT Membership Form

#### Name: [Blank]
#### Birthdate: / / 

#### Address: [Blank]

#### City: [Blank]  St/Province: [Blank]  Postal Code: [Blank]

#### Telephone HM: [Blank]  WK: [Blank]  Fax: [Blank]

#### E-Mail: [Blank]

#### Other: [Blank]

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### Annual Membership Classification

- **Patient** $50
- **Donor** $500
- **Advocate** $50
- **Sponsor** $1000
- **Professional** $100
- **Corporate** $1000
- **Other** $________
- **Include me as a PAACT member, though I currently cannot contribute**

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Tribute gifts support the daily operations of PAACT, Inc., by furnishing PC patients, doctors and advocates with the latest information available on the methods of detection, diagnostic procedures, evaluation and treatments for prostate cancer. We also participate in matching gift programs and United Way. For more information contact us at (616) 453-1477.

- **Check Enclosed**
- **Charge to my credit card (below):**
  - [ ] MC
  - [ ] VISA
  - [ ] Discover
  - [ ] American Express

**Enclosed is $ __________________________, a gift to the Lloyd J. Ney, Sr. Memorial Fund.**

**Enclosed is $ __________________________, for PAACT’s general operation expenses.**

**Enclosed is $ __________________________, I wish to remain anonymous.**

In Memory of __________________________________________________________________________________________

Please send acknowledgement card to:

**Name** __________________________________________________________________________________________________

**Address** __________________________________________________________________________________________________

**City** ____________________  **State** ____________________  **Zip** ____________________

**Account Number:** ____________________  **Amount $** ____________________

**Signature:** ____________________  **Expiration Date:** ____________________