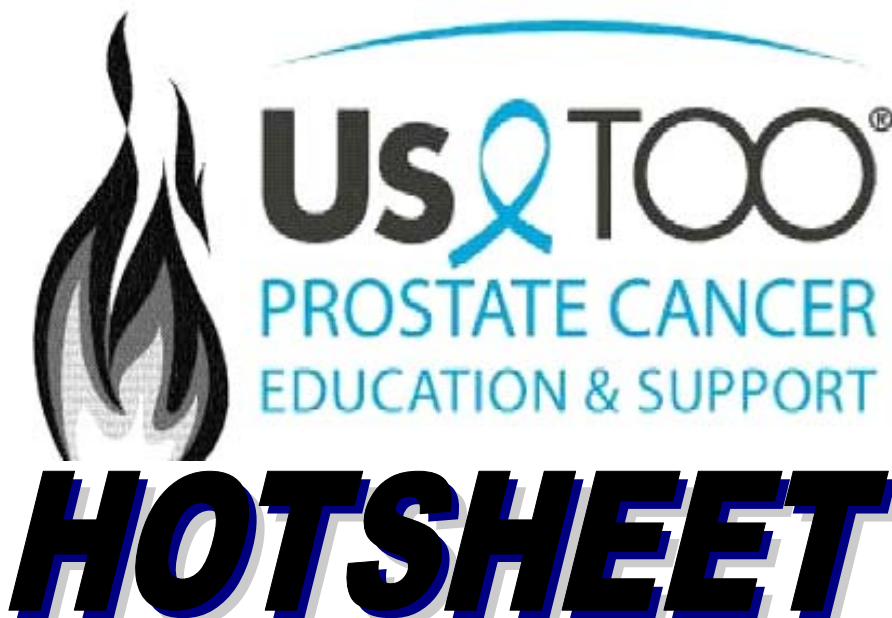


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FEBRUARY 2011

DUTASTERIDE ENHANCES PREDICTIVE USEFULNESS OF PSA TEST

The PSA test remains the most widely validated marker of prostate cancer risk. However, it is an imperfect screening tool, and in many cases it has led to unnecessary biopsy and overtreatment. In addition, its effect on prostate cancer mortality is also uncertain.

A new study published in the January 2011 issue of the *Journal of Urology* (vol. 185, pp. 126-31, 2011) suggests that the PSA test is more reliable in men taking dutasteride (Avodart®). Researchers found that even slightly increased PSA levels in men receiving dutasteride was a better indicator of clinically significant cancer compared with those men in the placebo group.

Data was analyzed from the REDUCE [Dutasteride of Prostate Cancer Events] study, which was initially conducted to evaluate the efficacy and safety of 0.5 mg dutasteride daily as a means of reducing prostate cancer risk. The study involved 8122 men between the ages of 50 and 75 years with PSA values between 2.5 and 10.0 ng/mL who had 1 negative prostate biopsy within 6 months before inclusion in the cohort.

In the current analysis, Dr. Gerald Andriole, the Robert Killian Royce Distinguished Professor and chief of urologic

(Continued on page 5)

IS PROSTATE CANCER IN OLDER MEN MORE DEADLY?

It's the most common cancer among men. Prostate cancer will affect one in five men at some point in their lifetime, usually men over the age of forty. Fortunately, most prostate cancers are relatively slow growing. On the other hand, a new study published in the *Journal of Urology* (Vol. 185, pp. 132-7, 2010) showed that older men with prostate cancer may have a more aggressive course.

When researchers looked at the records of over 12,000 men, they found that men older than age 70 with prostate cancer were more likely to have an aggressive course of disease than younger men. Not only that, but prostate cancer mortality was higher in these men.

Experts previously believed that most prostate cancers were slow growing even in older men, so most doctors advocated a less aggressive treatment approach for older men with prostate cancer due to their shorter overall life expectancy. This means that many older men haven't been offered radical prostatectomy (RP) or radiation therapy (RT) due to the belief that they'll die of other causes before their prostate cancer takes their life.

This new study calls this approach into question. With men living longer, healthier lives, older men with prostate cancer should be offered RP and RT to

(Continued on page 8)

US TOO NAMES NEW BOARD OFFICERS, ANOTHER MEMBER FOR 2011

At their December 4, 2010 meeting, the Us TOO International Board of Directors elected new officers for the coming year, and approved another new Board member. Continuing their service are Executive Committee members Fred Mills of San Antonio, TX, re-elected Chairman of the Board for the third year, Kay Lowmaster, MSW, LCSW, of Pittsburgh, PA, serving year two as Vice-Chair, and David Houchens, PhD, of Columbus, OH, also serving a second year as Treasurer. Ridge Taylor of Lake Oswego, OR, was elected Secretary, previously serving on the Executive Committee as Assistant Secretary/Treasurer last year.

Howard Kaczmarek of Rainier, OR, was appointed to serve a 3-year term beginning January 1, 2011. Mr. Kaczmarek is a prostate cancer survivor and advocate. Diagnosed with prostate cancer in 2001, he underwent a radical prostatectomy followed by several years of hormonal treatment, during which his PSA remained undetectable. He has been on a Lupron break since August 2009.

Kaczmarek is currently active in the Oregon Health and Science University (OHSU) Prostate Cancer Support Group, and the OHSU Prostate Cancer Program Advocacy Group. He serves on the Pacific Northwest Prostate Cancer

(Continued on page 3)

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5003 FAIRVIEW AVE. DOWNER'S GROVE, IL 60515
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POPULAR ONLINE PROSTATE CANCER TOOL QUESTIONED

The Cancer Risk Calculator for Prostate Cancer (PCRC), an online tool for clinicians, underestimates the probability that a patient may have an aggressive form of the disease and should be used with "caution," according to a new study published online 20 December 2010 in the journal *Urology*.

The PCRC incorporates the variables of race, age, prostate-specific antigen (PSA) level, family history, digital rectal exam, prior prostate biopsy, finasteride use, body mass index, and if it is available, PCA3, a newer urinary test. The calculator determines a level of risk for biopsy-detectable prostate cancer. The PCRC was initially developed using men from the placebo group of the Prostate Cancer Prevention Trial (PCPT), a large, 7-year, randomized controlled trial of finasteride, reported in 2003 by Dr. Ian Thompson and colleagues and sponsored by the National Cancer Institute. Dr. Thompson is a practicing urologist at the University of Texas Health Science Center at San Antonio, TX.

To assess the usefulness of the PCRC, the Stanford investigators used the statistical formula that generated the calculator's risk estimations. However, they used a different patient sample than Dr. Thompson and his fellow developers used. The authors stated that the "unreferred" men "without suspicion of prostate cancer" enrolled in the PCPT trial do not represent typical men referred to a urologist for risk assessment and possible prostate cancer biopsy. "Referred" men have a higher risk for prostate cancer, they say.

The study assessed the relative risk of men from the Stanford Prostate Needle Biopsy Database, all of whom were referred for suspicion of prostate cancer and were biopsied. An indicator of how different the PCPT and Stanford data sets are is found in their PSA and Gleason scores. The median PSA in the PCPT placebo group was 1.5 ng/mL, and median PSA in the Stanford cohort was 5.7 ng/mL. Also, the percentage of men with high grade disease was 7-fold higher in the Stanford cohort than in the original sample from the PCPT.

PSA, abnormal digital rectal examination, and family history were independent risk factors in the Stanford patients.

However, "our model predicted a much greater risk of high grade disease than the PCRC," write the authors. Both the Stanford and the PCPT analyses defined high-grade prostate cancer as that with a Gleason score of 7 or greater.

Dr. Thompson defended the tool and emphasized its positives. "This risk calculator has repeatedly been validated in multiple external populations and... substantially improves on the assessment of a man's risk of prostate cancer over just using PSA alone," he said. "The primary point of the PCRC," he added, "is that physicians cannot use PSA alone as they oftentimes do." Clinicians need to incorporate other risk factors in the decision about performing a prostate biopsy, Thompson stated.

Dr. Thompson also suggested the new study's findings were not outside the realm of possibility, given the "fundamentally different" population of men studied. Dr. Thompson also stated the PCRC is not a finished product. "We are constantly improving the calculator (and have recently included body mass index and the PCA3 urinary prostate cancer detection test), and so it will improve with time," he said.

Senior author Joseph Presti, Jr, MD, professor of urology, stated in a press release, by underestimating high-risk disease, the calculator fails to accurately estimate "just the kind of prostate cancer you want to detect as soon as possible." However, despite their objections about the PCRC, the Stanford investigators found that after crunching their own numbers, "our predictions of overall prostate cancer risk did not differ significantly from those of the calculator."

In an accompanying editorial, Dr. Stephen Eyre from the Beth Israel Deaconess Medical Center in Boston, MA noted that there are significant differences in ethnicity between the two study cohorts. The Stanford group had an unusually large percentage of Asian men, (10%) vs. an unknown percentage in the PCPT group, which could possibly account for some of the differences. It would be interesting to study further whether this particular ethnic group may contribute a higher percent of patients with high grade disease," he writes.

Medscape Medical News, 20 December 2010

NEW BOARD OFFICERS *(Continued from page 1)*

SPORE in Seattle, WA, and is a Consumer Reviewer for the Department of Defense Prostate Cancer Research Program. He has participated in several OHSU clinical studies regarding patients with prostate cancer, and in various Portland area fundraisers for prostate cancer education and research.



Howard Kaczmarek, New Director

He is a retired quality assurance / electrical engineer with extensive experience in the field of building and operating nuclear powered, electrical generating stations, and the construction of nuclear waste treatment facilities. Born and raised in the Chicago area, Howard has spent the last 20 years in the beautiful Pacific Northwest. Howard has been happily married to Karin for 46 years, has two grown daughters and one grandson, and makes frequent trips back to the Midwest to visit family and friends.

Continuing their service on the Us TOO International Board of Directors are: Jerry Hardy, Detroit, MI; Jean Jeffries, Meridian, ID; David Lubaroff, PhD, Iowa City, IA; Rick Lyke, Charlotte, NC; Jim Rieder, Powell, OH; Dexter C. Rumsey, III, Irvington, VA; Jack Shaff, Portland, OR; and Tom Kirk, President & CEO, Us TOO International, Downers Grove, IL.

The Board bid a fond farewell to two long-serving members, Greg Bielawski of Wheaton, IL, and Carl Frankel of Pittsburgh, PA, recognizing their dedication and exceptional service as they completed their terms on December 31, 2010. Us TOO International Board

Chair Fred R. Mills speaks of each:

“Carl Frankel, Pittsburgh, PA, served from January 2005 to December 2010. Carl’s legal background and his knowledge and expertise in legal matters were invaluable to the Board. Carl guided the Board as we were fortunate to receive several bequests in recent years. Carl served as Secretary to the Board and was the Chair of the Membership committee. We wish him the very best and look forward to having him involved in future committee activities.”



Carl Frankel, Esq., retires after serving 6 years on Us TOO Board

“Greg Bielawski, Carol Stream, IL served two years of an unexpired term from May 2003 – December 2004 and two elected terms from January 2005 to December 2010. Greg served as Treasurer and was a great asset to the Board and management because of his residence in the Chicago area. Greg represented Us TOO as co-chair of the organizing committee for the 2009 Chicago SEA Blue run/walk. Greg’s background in city management and budget oversight were especially helpful. We wish him the very best and also look forward to having him involved in future committee activities.”

“We will miss both of these prostate cancer survivors on our Board, but know that they will continue to help us keep the organization focused on our mission of helping men and their families make informed decisions about prostate cancer detection and treatment through support, education and advocacy.”



Greg Bielawski, retires after serving 8 years on Us TOO Board

The Annual Board Meeting dinner on Friday night featured the Bill Blair Memorial lecture by Rabbi Ed Weinsberg on “Not Tonight Dear – Sex after Prostate Cancer,” and included recognition of special corporate guests Catherine Bonetti from Accuray, Suzy Geroux from American Medical Systems, Janice King, PhD, from Medivation, and Mildred Kowalski, RN, PhD, from Novartis. Additional corporate representatives were in attendance for the Us TOO Prostate Cancer Business Leadership Council meeting, held prior to the dinner event, featuring a presentation by Jenny Carloss, Manager, Avalere Health, Washington DC, on “An Evolving Healthcare Environment.”

The highlight of the evening was the presentation of the 2010 Edward C. Kaps Hope Awards, given to outstanding chapter support group leaders nominated by their peers. Honorees included: Willie Cotton, retired Chapter Leader Us TOO Sierra Vista, AZ; George Melton, Chapter Leader Us TOO Peoria, IL; Henry Plunkett, Chapter Leader Us TOO Texoma, TX; Craig Schmidt, Chapter Leader Us TOO Mather Memorial Hospital, Port Jefferson, NY; Judi Sumoski, Chapter leader Us TOO Lancaster, PA; and Bill Whitmore, Chapter Leader of Us TOO Sunderland and Springfield, MA groups. More information about these tireless volunteers can be found in the January 2011 issue of the *Us TOO Chapter NEWS*.

CANCER BLOOD TEST CLOSER TO MARKET

A blood test so sensitive that it can spot a single cancer cell lurking among a billion healthy ones is moving one step closer to being available at your doctor's office. Boston scientists who invented the test and health care giant Johnson & Johnson have announced that they are joining forces to bring it to market. Four big cancer centers also will start studies using the experimental test this year.

Stray cancer cells in the blood mean that a tumor has spread or is likely to, many doctors believe. A test that can capture such cells has the potential to transform care for many types of cancer, especially breast, prostate, colon and lung. Initially, doctors want to use the test to try to predict what treatments would be best for each patient's tumor and find out quickly if they are working.

The only marketed test to find tumor cells in blood – CellSearch, made by J&J's Veridex unit – just gives a cell count. It doesn't capture whole cells that doctors can analyze to choose treatments.

Interest in trying to collect these cells soared in 2007 after a study was published regarding this test by Dr. Daniel Haber and his colleagues at Massachusetts General Hospital (MGH). It is far more powerful than CellSearch and traps cells intact. It requires only a cou-

ple of teaspoons of blood and can be done repeatedly to monitor treatment or determine why a drug has stopped working and what to try next.

"There's a lot of potential here, and that's why there's a lot of excitement," says Dr. Mark Kris, lung cancer chief at Memorial Sloan-Kettering Cancer Center in New York. He had no role in developing the test, but Sloan-Kettering is one of the sites that will study it this year.

The test uses a microchip that resembles a lab slide covered in 78,000 tiny posts, like bristles on a hairbrush. The posts are coated with antibodies that bind to tumor cells. When blood is forced across the chip, cells ping off the posts like balls in a pinball machine. The cancer cells stick, and stains make them glow so researchers can count and capture them for study.

The test can find one cancer cell in a billion or more healthy cells, says Mehmet Toner, a Harvard Univ. bioengineer who helped design it. Researchers know this because they spiked blood samples with cancer cells and then searched for them with the chip.

Studies of the chip were published in the journals *Nature*, the *New England Journal of Medicine* and *Science Translational Medicine*. It is the most promising

of several tests that companies and universities are developing to capture circulating tumor cells, says Bob McCormack, technology chief for Veridex.

"This is like a liquid biopsy" that avoids painful tissue sampling and may give a better way to monitor patients than periodic imaging scans, says Dr. Haber, chief of MGH's cancer center and one of the test's inventors. Ultimately, the test may offer a way to screen for cancer besides the mammograms, colonoscopies and other less-than-ideal methods used now.

Many people have their cancers diagnosed through needle biopsies. These often do not provide enough of a sample to determine what genes or pathways control a tumor's growth. Or the sample may no longer be available by the time the patient gets sent to a specialist to decide what treatment to prescribe. A test that can gauge success sooner, by looking at cancer cells in the blood, could give patients more options. "If you could find out quickly, 'this drug is working, stay on it,' or 'this drug is not working, try something else,' that would be huge," Haber says.

Already, scientists have been surprised to find that more cancer patients harbor

(Continued on page 6)

OLDER MEN GET LESS EFFECTIVE PROSTATE CANCER CARE

Old age is no hindrance to benefiting from prostate cancer surgery and radiation therapy, according to a new US study in the 6 December 2010 *Journal of Clinical Oncology* online edition. The results of that study shows men over 75 often get less effective treatment than their younger peers.

"It seems men in this age group are often undertreated, and that in turn may contribute to the higher mortality from prostate cancer among older men," said Dr. Matthew Cooperberg of the University of California, San Francisco, who led the research.

Cooperberg and colleagues reviewed data from 40 urology practices across the US, including nearly 12,000 patients with prostate cancer. They found 60 percent of those aged 75 and over received only hormone treatment for high-

risk tumors, even though that's not considered a cure, and eight percent were followed by their doctors with no active treatment. By contrast, hormone treatment for such cancers was given to just between 18 and 26 percent of younger patients, and no more than one percent of them were put on watchful waiting.

At first glance, age appeared to be tied to cancer deaths, suggesting older men fared worse. But when researchers adjusted calculations based on the type of treatment, age no longer mattered.

Among 629 men aged 70 and older with high-risk cancer, about one in five died of prostate cancer within six years of their diagnosis. Those who had so-called local treatment – such as prostate cancer surgery or radiation – were 46 percent less likely to die from their cancer than those who had hormone therapy or were

put on watchful waiting.

"If you look at the national practice pattern, there is no question that older men are treated very differently," Cooperberg said. "Age is a stronger driver of treatment pattern than risk, and I think that's troubling." Men with low-risk disease often do fine without aggressive treatment, he added. "Treatment really should be guided by disease risk, not by patients' chronologic age."

So far, there are no randomized studies to demonstrate that local treatment actually makes men less likely to die from cancer, but observational studies hint of it. And since all treatments come with side effects – the right treatment option should be considered on a patient-by-patient basis, doctors say.

Reuters Health, 8 December 2010

DECISION MAKING IN LOCALIZED PROSTATE CANCER: LESSONS LEARNED FROM AN ONLINE SUPPORT GROUP

Huber J, Ihrig A, Peters T, et al
BJU Int, 24 November 2010
Epub ahead of print

To investigate patient-to-patient communication with regard to decision-making in localized prostate cancer; as most of it is done in private, online support groups are a unique means for this task.

Over a 32-month period, we screened 501 threads in the largest German online support group for prostate cancer. Threads started by questioners newly diagnosed with localized prostate cancer and stating decision-making as the key topic were included; in all, 82 (16.4%) threads met these criteria. Two independent investigators characterized every thread following a standardized protocol. Fisher's exact test and Mann-Whitney U-test were applied for group analyses. A complementary qualitative linguistic approach was chosen.

Threads were most commonly started to ask for therapy recommendations (66%), information on the course of treatment (46%) and emotional support (46%). Answers consisted of treatment recommendations (40%), emotional support (37%) and personal experiences (28%). A second opinion on the biopsy cores (51%) and additional imaging (40%) were common suggestions. The rate of advice for radical prostatectomy (RP) vs. radiotherapy was 67 vs. 82%. Thus, surgery was less recommended in our sample (P= 0.01); 75% of the men with an initial therapeutic preference were finally confirmed herein. Linguistic analysis showed that posters frequently use a tentative language style and that common language is avoided.

Patients readily receive information, advice and emotional support as part of an online support group. The scientific evaluation of an online support group is a complementary way of getting to know our patients' needs and worries. Patient-physician contact can benefit from this knowledge.

DUTASTERIDE ENHANCES USEFULNESS OF PSA TEST

(Continued from page 1)

surgery at Washington University School of Medicine, St. Louis, MI and colleagues evaluated whether dutasteride use enhanced the usefulness of total PSA for diagnosing clinically significant prostate cancer.

Participants in the REDUCE trials had been randomly assigned to receive either dutasteride or placebo, and total serum PSA was assessed every 6 months. In addition, participants underwent 10-core transrectal ultrasound guided biopsy at 2 and 4 years; unscheduled biopsies were also performed if there was a clinical indication to warrant performing one.

Among those who underwent at least 1 biopsy, prostate cancer was detected in 659 men (19.9%) in the dutasteride group and 858 (25.1%) in the placebo group (P <0.0001). Of these cancers, 220 (6.7%) were Gleason score 7 to 10 in the dutasteride group and 233 (6.8%) in the placebo group (P = 0.81, not statistically significant).

At 6 months, the PSA of dutasteride users was reduced by a mean of 46.9% in men without cancer, by 45.4% in men with Gleason score 5 to 6 cancer and 46.3% in men found to have Gleason score 7 to 10 cancers. In both treatment groups, mean PSA levels were highest in men eventually diagnosed with Gleason 7 to 10 cancers but were similar in those diagnosed with low-grade cancers or found not to have cancer.

The authors note that baseline PSA was a "poor predictor of the future diagnosis of any prostate cancer" (P = 0.42) or Gleason score 7 to 10 prostate cancer (P = 0.79). PSA levels rose during the study period in 72% of men receiving placebo, but only 29% of those receiving dutasteride. As compared with no increase in PSA from month 6 to the final PSA in men who received dutasteride, the authors write, "an increase in PSA was associated with a higher likelihood of biopsy detectable prostate cancer (any grade and Gleason score 7 to 10) and greater likelihood of a clinically significant tumor."

The final PSA was also a relatively poor predictor of prostate cancer of any Gleason score, but better predicted disease with Gleason score 7 to 10 in both treatment groups. Final PSA was significantly higher with dutasteride group than placebo (any Gleason score, P = 0.0020; Gleason score 7 to 10, P = 0.0491).

Dr. Andriole said that dutasteride may make the PSA a more effective screening tool for prostate cancer. "Overall, I think it will improve PSA screening, as it will tend to reduce the number of negative biopsies which are often triggered by the slow rise of PSA, due to benign growth of the prostate," he said. "Clinicians need to be aware that they should interpret PSA differently for men on dutasteride and finasteride (Proscar®) than for men not taking those medicines."

Medscape, 21 December 2010

CATCHING UP WITH THE PINK: LEATHER WRISTBANDS HELP RAISE AWARENESS, FUNDS FOR US TOO

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Editors' note: In the spirit of information sharing, we have invited certain physicians and others to provide comments and opinions for Us TOO's *HotSheet*. It is our desire to enrich the content of the *HotSheet* to empower the reader. The columns by Drs. Chodak, Moyad and Myers contain the opinions and thoughts of its author and is not necessarily those of Us TOO International.

ASK DOCTOR SNUFFY MYERS

In the "Physicians Who Cut Corners" post on your vlog <<http://askdrmyers.wordpress.com/2010/12/15/physicians-who-cut-corners/>> you said the 80 year old had a prostatectomy to start with and at the end you refer to a DRE. Are you saying that continuing with a routine DRE is recommended even though the prostate gland is gone?

Yes, that was the whole point of the video. It would have been malpractice for me not to do a rectal exam. Why? This man had had a PSA that was steadily increasing after a radical prostatectomy. In men with a slowly progressing PSA post surgery, the most common place to find the cancer is in the prostate bed.

This is the very reason why adjuvant radiation after surgery focuses on the prostate bed. Thus, as this man presented to our clinic, the odds were very high that his recurrent cancer was in the prostate bed. Thus, the rectal exam was the most important thing I could do at that visit. And, surprise, I found a fairly large cancer mass in the prostate bed. Subsequent radiation therapy has rendered him free of detectable cancer and an undetectable PSA.

So, let me repeat, a DRE is a very important part of the medical exam in a patient who has had a radical prostatectomy and has an elevated PSA. Physicians who do not do this exam are cutting corners at the patient's expense or simply do not understand the natural history of prostate cancer.

You know, we live in an exciting time. We have sequenced the human genome. Following this, we are in the process of finding the genes that determine whether your cancer will be dangerous or not. We even will soon be able to pick drugs for you based on a genetic analysis of your cancer. We have an FDA-approved prostate cancer vaccine and exciting new drugs in development. Yet, sometimes we do not need all of this great science, sometimes it only takes a finger up a patient's rectum to save his life.

DOC MOYAD'S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS "NO BOGUS SCIENCE" COLUMN "Creatine Supplements may reduce the side effects of cholesterol lowering drugs?"

Mark A. Moyad, MD, MPH,
University of Michigan Medical Center, Department of Urology

Bottom Line:

Creatine supplementation in small amounts may prevent some of the muscle pains associated with statins.¹

Michigan got beat ugly in our bowl game, our coach got fired, Coach Harbaugh went to the 49ers instead of Michigan despite being one of my classmates in grade school in Ann Arbor (why doesn't he like me/us?), and even Ohio State players got suspended for next season, but at least the Us TOO newsletter is something that you can still depend on every year!

There is so much talk lately about taking heart healthy products if you have prostate cancer and you know I have always been a fan of this approach. Aspirin is getting attention (future column), but cholesterol-lowering drugs (aka "statins") have more research. Some individuals have real problems taking statins because they can cause muscle aches and pains and there are not many solutions to preventing this problem. Switching the drug itself, or how often you take it, or just taking it with a meal have all been suggested. CoQ10 supplements (100-200 mg/day) may help prevent these side effects, but the research benefit is not consistent, and CoQ10 can be as expensive as Coach Harbaugh's next contract.

What to do? Despite being a very tiny human study (12 patients not able to tolerate statins) there was an interesting preliminary study published in a major medical journal recently that received little to no attention. Individuals taking 10 grams (only 2 teaspoons with 8 ounces of water per teaspoon) of the over the counter dietary supplement "creatine monohydrate powder" for 5 days (loading phase), and then taking just 5 grams (1 teaspoon with 8 ounces of water) daily with their statin drug (maintenance phase) had a reduction in

muscle pain. Creatine is needed in the muscles for energy and it is theoretically possible that statin drugs deprive muscles of this important nutrient. It could have also been a placebo effect, but who cares! Creatine has been around forever (shop around cause prices vary a lot) and has a great safety record especially at these low doses so it may be worth a try. P.S. This will be my last column for Us TOO if Michigan offers me the head football coaching position ("Coach Moyad"---Wow! Now that sounds good, especially if they would be willing to pay me and they understand that I have a vast level of coaching experience, especially when it comes to sitting on the couch in my living room and yelling at my television! No one does it better than me!).

Reference:

1. Shewmon DA, Craig JM. *Ann Int Med* 153:690-2, 2010

CANCER BLOOD TEST

(Continued from page 4)

these stray cells than has been believed. In one study, the test was used on men thought to have cancer confined to the prostate, "but we found these cells in two-thirds of patients," Toner says.

This might mean that cancer cells enter the blood soon after a tumor starts, or that more cancers have already spread but are unseen by doctors.

Or it could mean something else entirely, because researchers have much to learn about these cells, says Dr. Minetta Liu, a breast cancer specialist at Georgetown Univ.'s Lombardi Comprehensive Cancer Center. She led a session on them at the recent San Antonio Breast Cancer Symposium and has been a paid speaker for Veridex. She hopes the cells will someday aid cancer screening.

(Continued on page 8)

DOCTOR CHODAK'S BOTTOM LINE (Ref Key: Article #, page #, column #)*Author: Winning The Battle Against Prostate Cancer, 2011*

#2p1c2: The article suggesting that older men are at higher risk of dying from the disease presents a real challenge in terms of the take home message. First, the article suffers from being a retrospective analysis spanning 20 years yet the average follow-up is only 6 years, which is quite short. These two factors make reliability of the data quite questionable.

The findings also contradict those from the Swedish randomized study showing no benefit from radical prostatectomy for men over 65 compared to watchful waiting at least during the first 12 years.

It is exactly these discrepancies that make conclusions from retrospective studies so difficult to interpret. The authors also suggest that these findings challenge the idea of not screening older men but this study really does not prove that more aggressive screening would be beneficial.

The Bottom Line: This article does not provide strong justification to be more aggressive in older men but those with a Gleason 8-10 cancer do have a greater risk from the disease and should be made aware of this risk when being counseled about their options.

#6p4c2: The importance of treating high-risk disease is also addressed in the study reported by Cooperberg and co-workers. Do older men get inferior treatment because they are less likely to be offered curative therapy? One thing that is clear from watchful waiting studies is that men with a Gleason 8, 9 or 10 cancer have a significant risk of dying even within 5 years so they do not need to live 10-15 years to benefit from aggressive therapy. The Gleason 7 cancers are more uncertain.

The challenge for each patient is to understand the odds their treatment will be beneficial to them vs. the odds of side effects. What is unclear from the study is the extent to which men with higher-grade disease were presented enough information to make a decision and found that that the benefits were not enough to justify the risks. Unfortunately, without a randomized study, the value of aggressive treatment cannot be determined for the older men.

The Bottom Line: High grade cancers pose a more immediate risk to survival even in older men so careful counseling is needed so that men decide if they want to undergo aggressive treatment. Age alone should not be the reason to avoid aggressive therapy.

BIS: The article about Px SCORE as a postoperative assessment tool raises many questions about its potential use. Although it does appear to be a better predictor of PSA recurrent disease than pathological findings alone, at this time no information is available to tell what to do with the results.

Results of a randomized study showed that postoperative radiation for men with a positive surgical margin improves survival but about only about 1 out of 12 men benefit. Without further studies, there is no way to tell if this test can better identify which men should get radiation and what is the marginal benefit.

Hopefully more information will be forthcoming but at this time the data do not show that men will benefit from having this test done.

The Bottom Line: Men faced with a positive surgical margin after radical prostatectomy have a difficult decision to make. Radiation will help less than 10% live longer which means more than 90% are getting treated without benefit. A test that can tell who will benefit would be very helpful, but at this time such a test is not available.

#5p4c1: There also is a great excitement over a new test that can find a single cancer cell in a blood sample. It has the potential to be used for diagnosis, determining if a cancer is localized or how a patient is responding to treatment. Additional clinical testing is now proceeding and will be anxiously awaited.

And yet, there is an important reason to be cautious. For years, doctors have found that cancers seed cells into the blood stream but without any consequence. Tests developed in the past were finding cancer cells in the blood stream but subsequent studies failed to show their usefulness. Having cancer cells in the blood is a necessary requirement for

(Continued on page 8)

PROSTATE CANCER TREATMENT MAY BE TIED TO CATARACTS

Older men who opt for hormone-blocking therapy to treat prostate cancer might be slightly raising their risk of developing cataracts, hints new research reported on 26 November 2010 online ahead of print in the *Annals of Epidemiology*. However, it is not yet clear if the therapy does actually cause the clouding that develops in the lens of the eye.

So-called "androgen deprivation therapy," or ADT, suppresses production of testosterone. An estimated one of every three men with prostate cancer undergoes ADT, either in the form of drugs, such as Lupron® or Zoladex®, or surgery to remove the testicles.

Yet, it is increasing being recognized that ADT carries serious potential risks – namely, diabetes and obesity. Because both obesity and diabetes have been linked to cataracts, "we suspected that cataracts might have been another unintended consequence" of ADT, stated Jennifer Beebe-Dimmer of the Karmanos Cancer Institute in Detroit, MI.

To test their hunch, Beebe-Dimmer and her colleagues studied nearly 66,000 prostate cancer patients aged 66 or older from a large US cancer registry. In this group, nearly half of the patients had received some form of ADT within the first six months of their diagnosis.

Overall, about 111 new cataracts were diagnosed for every 1,000 men studied per year. After accounting for other risk factors, they found that men treated with ADT drugs had, on average, a 9 percent increased risk of developing a cataract compared to those not treated with ADT. The risk rose by around 26 percent for the far smaller proportion of men who had their testicles removed.

The increased risk is relatively small, noted Beebe-Dimmer. "With ADT so commonly used as part of a patient's treatment for prostate cancer, it's important to have a complete understanding of the negative consequences of therapy," she said. "Patients should be monitored carefully while on ADT for new diagnoses of diabetes, and potentially cataract," Beebe-Dimmer added.

Reuters Health, 27 December 2010

CANCER IN OLDER MEN*(Continued from page 1)*

potentially cure their prostate cancer, especially if they're otherwise healthy. This study showed that men have lower prostate cancer mortality when they're treated with RP and RT.

According to studies, prostate cancer mortality is a third lower in men who are treated aggressively with RP and RT. Considering a man 70 years old who is in good health can expect to live, on average, 13 more years, there's reason to consider more aggressive treatment for older men with prostate cancer. This also raises the question of when screening for prostate cancer in older men should stop. The researchers in this study emphasize that age shouldn't be the determining factor.

These days, age shouldn't be the determinant of how aggressively men with prostate cancer are treated. With average life-span rising, healthy men over the age of 70 still have enough good years left that they should be able to enjoy them free of prostate cancer.

<www.healthmad.com> (source – Reuters)
31 December 2010

CANCER BLOOD TEST*(Continued from page 6)*

“The dream is, a woman comes in for her mammogram and gets a tube of blood drawn,” so doctors can look for cancer cells in her blood as well as tumors on the imaging exam, she says.

The agreement will have Veridex and J&J's Ortho Biotech Oncology unit work to improve the microchip, including trying a cheaper plastic to make it practical for mass production. No price goal has been set, a company official says, but the current CellSearch test costs several hundred dollars.

The companies will start a research center at MGH and will have rights to license the test from MGH, which holds the patents.

In a separate effort, MGH, Memorial Sloan-Kettering Cancer Center, MD Anderson Cancer Center and Dana-Farber Cancer Institute will start using the test this year. They are one of the “dream teams” sharing a \$15 million grant from the Stand Up to Cancer telethon, run by the American Association for Cancer Research.

Associated Press, 3 January 2011

THE BOTTOM LINE*(Continued from page 7)*

cancers to spread but many other things must happen for it truly to be important.

The Bottom Line: Hopefully this test will continue to show promise but at this time much more data is needed before its value can be determined. Men should not be in a hurry to have this done.

#10p7c3: A recent study suggests yet another potential adverse effect of androgen deprivation might be the development of cataracts. The data was obtained from Medicare patients but not from a well designed study. As a result, no firm conclusions are permitted.

Given that several randomized studies having been conducted in men getting radiation therapy, there might be an opportunity to find out if indeed this relationship is correct.

The Bottom Line: Until more data are forthcoming, men on ADT may warrant being checked for cataracts but better data are needed to know if there truly is an added risk. If it turns out to be true, then it adds one more reason why men should not get hormone deprivation unless they are appropriate candidates.

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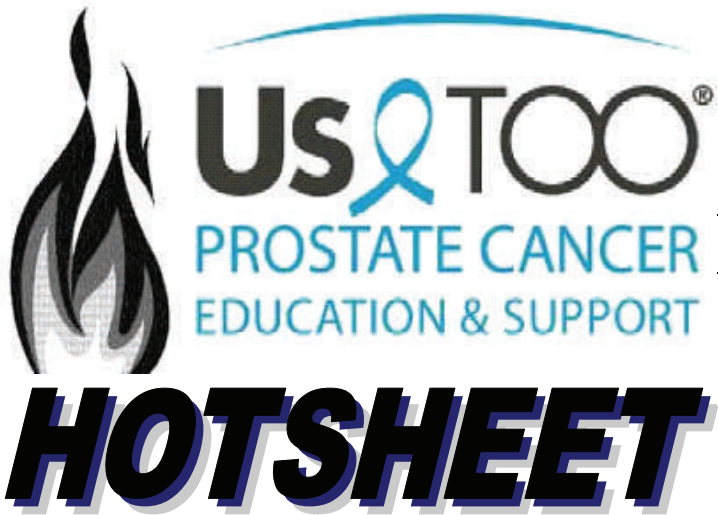
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A SYSTEMS PATHOLOGY APPROACH TO POST-SURGICAL PATIENTS WITH ANXIETY

Jason M. Alter, PhD

Introduction

In 2010, approximately 218,000 men were diagnosed with prostate cancer and, based upon available data, approximately 50% of men opted for surgery.^{1,2} Radical prostatectomy (RP) is considered the gold standard by many physicians and it is indeed effective for the vast majority of those treated. However post-surgery, a number of men have higher risk features such as positive surgical margins (incidence ranges from 11% to 46%) or extracapsular extension which cause these men concern and require physician counseling.³

Typically, positive surgical margins (PSMs) are defined as the presence of tumor at the inked margin of the removed specimen and extracapsular extension (ECE) is defined as tumor extending from the prostate into the periprostatic tissue.⁴ After RP, the prostate is sent to the pathology laboratory. Technicians process the tissue and a pathologist examines the specimen, grading the tumor and assessing the extent of the disease. Often the prostatectomy Gleason score differs from the Gleason score assigned at biopsy. This is because the biopsy view is an extremely narrow perspective of the tumor whereas, after surgery, the entire prostate can be assessed. It is during the pathologic review of the prostatectomy tissue that the presence of PSMs or ECE is determined.

There are several obstacles to understanding the actual risk posed by a PSM. The presence of a PSM is determined by a pathologist but it is a subjective assessment and can be difficult to un-

equivocally ascertain due in part to variables such as anatomic location and specimen processing. A PSM can be due to an extensive tumor but, in certain locations (such as posteriorly against the rectum or laterally against the pelvic sidewall), there is a limit to the amount of tissue a urologist can remove; in these sites pathologists cannot be certain how much tumor, if any, is truly at the inked margin and therefore still in the patient.⁴ In addition, a PSM can result from an incision through a tumor that is outside the prostate capsule, or by an accidental incision into the prostate in a case that is actually organ confined disease. Other research has suggested that the tissue preparation method, used in the pathology laboratory, may result in different PSM rates.⁵

Given the subjective and variable nature of what may constitute a PSM, it is not surprising that the association of increased risk between a PSM and post-RP prostate cancer recurrence (measured primarily as biochemical or PSA recurrence) has resulted in variable outcomes in the literature. Most studies, but not all, find an association between PSM and PSA recurrence.^{6,7} Studies have analyzed the possible cancer recurrence risk with many aspects of PSMs. Many believe that positive margins in specific locations place a patient at higher risk but research conflicts on this point.^{5, 8-10}

Other studies suggest that margin length or the number of positive margin sites may or may not be associated with higher risk.^{5, 11-12} Some have found an association between PSM, the need for salvage therapy and decreased risk of

survival.^{13, 14} However, PSMs typically become less predictive when other factors such as high Gleason score (≥ 8) or seminal vesicle invasion (SVI) are factored into the analysis.^{6, 14}

Regardless of the exact nature of the positive margin or the link to cancer recurrence, margin status can affect treatment management.¹⁵ Some advocate adjuvant therapy for patients with PSMs and although results are controversial more studies continue to be published on the potential benefits of adjuvant therapy for patients with pathologically advanced prostate cancer.¹⁶⁻¹⁹

Post-RP patients, who experience a high-risk feature, regardless of its nature (PSM, ECC or high Gleason score) or have any concern, benefit from having an objective, comprehensive and more accurate understanding of their real risk of serious disease progression. New tools that incorporate a patient's molecular and cellular information provide a personalized risk assessment that can be very important during counseling post-surgery. One such 'tool' is Aureon's Systems Pathology approach: an objective integration of multiple types of data that results in personalized patient risk assessment. Traditional pathology bridges both basic and clinical biomedical sciences. However, there is a degree of subjectivity to these analyses, and they lack the ability to provide measurable results. Aureon's Systems Pathology approach overcomes these deficiencies by integrating information from tissue shape and patterns, clinical data and the cellular localization and measurement of molecular information.

What is Post-Op Px?

Post-Op Px™ is an innovative test, based upon Systems Pathology that provides each post-surgical patient with an objective, comprehensive and personalized assessment of their risk. When a urologist orders Post-Op Px, Aureon sends a request to the pathology laboratory that processed the prostatectomy sample. The laboratory sends the tissue and the results of their pathology determination to Aureon for subsequent prognostic analysis. Aureon pathologists and scientists use a patented technological approach that combines image analysis, protein detection, clinical/pathologic information and mathematics to uniquely measure:

- The tissue patterns of each patient's surgically removed prostate tumor
- Biologically-relevant proteins in the tumor specimen

Post-Op Px helps predict:

- Patients likely to have serious disease progression (metastasis, or salvage therapy failure) within 5 years of RP
- Patients likely to have PSA recurrence within 5 years of RP

Patients with PSMs may be anxious. These men or their loved ones do research on the Internet. They ask their doctor many questions about their status and the extent to which they should be concerned. There is a range of medical responses to PSMs: some physicians wait for the PSA to rise before becoming concerned, others watch the patient closely or are not concerned, and yet others consider adjuvant therapy. The difficulty arises from the subjective nature of surgical margins (see intro) and the extent of risk that a PSM may or may not pose for the individual. Post-Op Px provides an additional and objective perspective about the person's likelihood of serious disease progression.

How was Post-Op Px developed?

A cohort of 881 patients and associated outcome data was assembled from Memorial Sloan-Kettering Cancer Center. After review, there were 758 evaluable cases in the cohort. The median time to disease progression was 5 years post-RP. The cohort was split into demographically balanced data sets. One data set was used to design and develop Post-Op Px and the second data set was used

to independently validate the test's ability to predict disease recurrence and progression.

Post-Op Px Reimbursement

Aureon currently bills all commercial, private, third party carriers, and Medicare. Our Aureon Patient Care Program – APCP can be helpful to patients in understanding the reimbursement process. Aureon feels very strongly that no patient should ever be penalized financially while working through their battle with Prostate Cancer. Aureon's billing dept does offer an up-front benefit investigation if required to get general info regarding deductibles and coinsurance.

Comparison of Systems Pathology with Post-Surgical High Risk Features

In initial studies, Post-Op Px was able to accurately separate low-risk and high-risk patients for both advanced disease progression and PSA recurrence using the patient's own RP sample.^{20, 21}

Given the possible significance of PSMs and ECE with disease progression an analysis was conducted utilizing the Post-Op Px validation data set to investigate the comparison of these pathologic features with the Post-Op Px integrated, Systems Pathology approach for predicting outcome. A sub-cohort study was conducted utilizing the Post-Op Px validation data set to investigate the comparison of these pathologic features with the Post-Op Px integrated, Systems Pathology approach for predicting outcome.²²

Prognostic accuracy was measured by both hazard ratio (HR) and concordance index (CI). The HR is a measure of the effectiveness of a factor/variable to stratify patients into different risk populations: low- and high-risk. An HR of 1

means there is no difference in risk between the two groups. An HR of >1 means patients in the predicted high-risk group are indeed at higher risk than the predicted low-risk group. As the HR increases, the more accurate the low/high risk stratification.

The CI is the probability that, given two randomly selected patients, the patient with the worse outcome is, in fact, predicted to have a worse outcome. This measure, similar to an area under the receiver operating characteristic curve, ranges from 0.5 (i.e., chance or a coin flip) to 1.0 (perfect ability to rank patients). The higher the CI the more accurate the test performs.

An analysis of the disease progression endpoint (Table 1) in the validation cohort (N=385) examined the HR, CI and associated p values of clinical and pathologic variables in comparison to the Px SCORE.

As Table 1 shows, age, clinical stage, pre-op PSA, RP Gleason sum, PSM, and ECE have poor prognostic value for disease progression, which in some cases, is not statistically significant (p-value >0.05). The Px SCORE has the best HR (11.4), which was highly statistically significant (p-value <0.0001), as well as the most favorable CI (0.84).

A similar analysis of the PSA recurrence endpoint (Table 2) in the validation cohort (N=340) examined the same performance metrics. As seen with disease progression, Table 2 also demonstrates that the Px SCORE possessed the best hazard ratio (HR 5.56), which was highly statistically significant (p-value <0.0001), as well as the most favorable concordance index (CI 0.77).

Table 1: Px SCORE Compared with Post-RP High-Risk Features

Predictor	CI	HR	P-value
Age	0.51	0	0.99
Clinical Stage	0.61	1.72	0.15
Pre-RP PSA	0.57	1.51	0.37
Post-RP Gleason score	0.68	2.28	0.08
SVI	0.64	5.90	<0.0001
PSM	0.60	2.34	0.03
ECE	0.61	2.29	0.03
Px SCORE	0.84	11.4	<0.0001

Another way of comparing high-risk features and the Systems Pathology approach is a Kaplan Meier survival curve. As seen in Figure 1, Post-Op Px is better able to separate high from low risk patients for disease progression in 5 years than surgical margin status.

Conclusion

Post-surgical patients with a high risk feature(s) have understandable questions and concern. The literature demonstrates the difficulty in extrapolating from a patient’s risk feature to actual disease prognosis. Better tools are needed to help provide more information about each patient’s specific circumstance. Aureon’s System’s Pathology approach, exemplified by Post-Op Px, supports the belief that more comprehensive, advanced prognostic tools require the integration of multiple features at the molecular and cellular level.

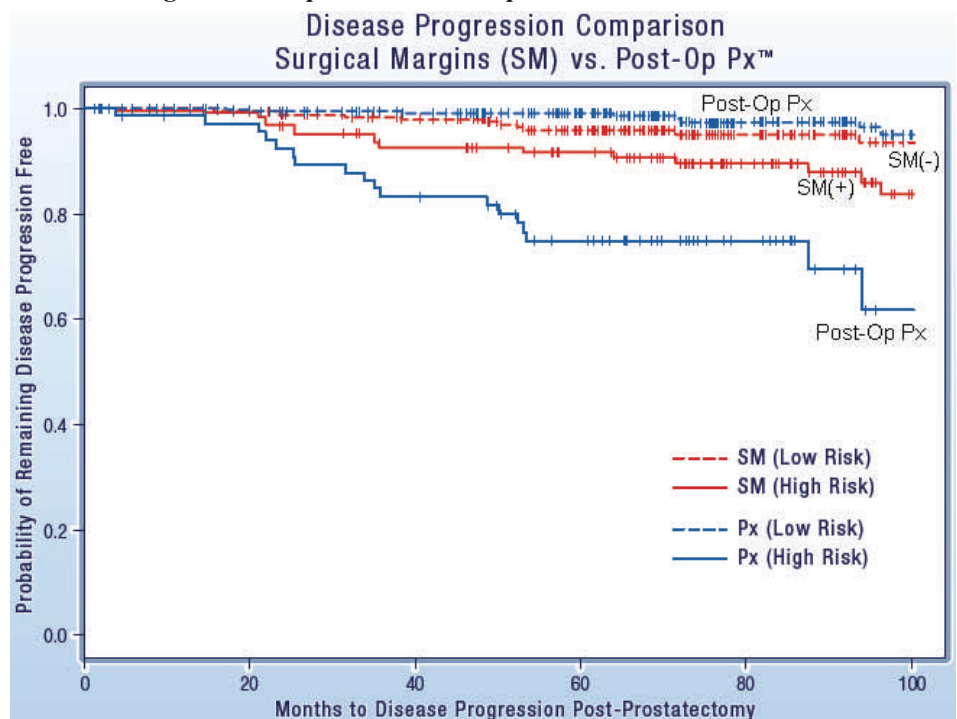
Systems Pathology provides a more accurate and objective prediction of serious disease progression than methods that rely primarily on clinical and pathologic features. Post-Op Px enables physicians to properly assess serious disease progression risk (metastasis, failure of surgery and salvage therapy within five years) post-RP.

Any surgical patient can benefit from this information but, especially, patients with a high risk feature(s) as well as their physicians will benefit from an objective perspective that provides new information for their personal risk assessment. Post-Op Px is an important tool during patient counseling.

Table 2: Prediction of Post-RP PSA Recurrence

Predictor	CI	HR	P-value
Age	0.59	0	0.99
Clinical Stage	0.64	1.99	0.02
Pre-RP PSA	0.65	2.60	0.01
Post-RP Gleason Score	0.70	4.70	0.001
SVI	0.56	3.38	0.003
PSM	0.65	3.75	<0.0001
ECE	0.68	4.29	<0.0001
Px SCORE	0.77	5.56	<0.0001

Figure 1: Comparison of Post-Op Px to Post-RP PSM Status



Editor’s Note: Other tools are available to assist physicians in counseling a patient who is found to have high-risk features on final pathologic exam of the excised tumor. These include predictive algorithms and nomograms that estimate risk using a variety of pre-RP and post-RP risk factors collected from patient cohorts. Many utilized data from RP patients treated at one or more prostate cancer surgical centers of excellence and are accessible at no charge on the Internet. The CIs of such methods range from 0.7 to 0.85 depending on the model used¹ and showed comparable CIs to earlier Systems Pathology software versions.² Like the Px SCORE, results with these nomograms have been independently

validated. One drawback, however, is some models overestimate recurrence risk in men with higher risk features.³ Various tumor markers have been incorporated into the pre-RP and post-RP risk assessment models predicting post-RP PSA progression. Markers utilized in predictive models include human glandular kallikrein-2 (hK2),⁴ PSA isoforms such as free PSA and [-2]pro-PSA⁵ and serum proteomic biomarkers.⁶ Another exciting prognostic tool for predicting cancer outcome is the detection and quantification of the number of circulating tumor cells (CTCs) in patients with solid tumors (including prostate cancer).⁷⁻⁹ Surprisingly, CTC detection rates and CTC numbers were inde-

pendent from disease stage. Various immunocytochemical enrichment methods are available⁷ and RT-PCR can be used to quantitate circulating levels tissue-specific mRNA transcripts.⁸ CTCs can be detected before, during and after RP for localized disease. However, the likelihood of developing biochemical progression or distant metastasis in early stage patients seems to be higher when tumors cells persistently reside in the patient bone marrow.⁹ In advanced disease, CTC measurements serve as an excellent prognostic tool. It is important to note, however, that all tests mentioned here predict PSA recurrence, and not serious disease progression that the Post-Op Px test does.

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Editor's Note: See also the Feb 2011 issue of the *Us TOO HotSheet*, pg 4, for an article on circulating tumor cells and a new, sensitive blood test, *Cancer Blood Test Closer to Market*.