US TOO PROSTATE CANCER EDUCATION & SUPPORT
HOTSHEET

SPECIAL BURNING ISSUES SUPPLEMENT

SEPTEMBER 2009

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THIS SUPPLEMENT TO THE *US TOO PROSTATE CANCER HOT SHEET* WAS MADE POSSIBLE BY A CHARITABLE CONTRIBUTION FROM

AUREON LABORATORIES

IDENTIFYING CLINICALLY SIGNIFICANT PROSTATE CANCERS

INTRODUCTION

Welcome to this Us TOO *HotSheet* Burning Issues Supplement. Us TOO's Editorial Team periodically produces these Supplements to communicate timely, personalized and reliable information on specific issues relevant to prostate cancer that are of current interest or are subjects of controversy.

This month's Burning Issue surrounds the controversy engendered by the two recently published prostate cancer screening trials – showing a reduction in prostate cancer death in men who were screened – but also a significant risk of overdiagnosis. This again raised the most important unanswered question – how to predict whether a newly diagnosed, early-stage prostate cancer will behave like a "pussycat" or like a "tiger" in terms coined by Dr. Donald Coffey. The research community ardently seeks to discover new cancer biomarkers to solve this dilemma.

The main issue of this month's *HotSheet* also contains relevant articles as well, such as the article "Know Your Type" emphasizes the concept of risk assessment (low, intermediate or high for prostate cancer death) for newly diagnosed men considering treatment vs. active surveillance for their disease.

Another article reports the results of a European survey exploring anxiety in men undergoing active surveillance. Anxiety during active surveillance is the primary reason men abandon this effective treatment option. In this survey, 20% of men experienced significant anxiety and difficulty coping with their treatment choice.

(Continued on page 3)

THE PROSTATE CANCER SCREENING CONTROVERSY

Charles "Snuffy" Myers, MD

Recent science notwithstanding, prostate cancer screening remains controversial. One major question that fuels this controversy is whether screening saves lives. This year European scientists from the EORTC published the first randomized clinical trial that adequately addresses this question. This trial had enough patients enrolled, and extended just beyond 12 years. The results showed that screening for prostate cancer does save lives and that it's comparable to other widely used cancer-screening tests. I quote:

"The number needed to screen (to save a life) in our study is similar to that in studies of mammographic screening for breast cancer and fecal occult-blood testing for colorectal cancer."[1]

As the authors concluded, this study probably underestimates the value of prostate cancer screening. First, with only 12 years of follow up, it is too early to see the full benefit. In fact, the difference between the screened and the control group is still widening. Second, patients were screened every 4 years, which is too infrequent for more aggressive forms of prostate cancer. For those interested, we have published a detailed analysis of this screening study and its implications. You can go to <www.prostateforum.com> or call +1 434 974-1303 to receive it.

As with most good clinical trials, this study generates more questions than answers. One common problem is that a significant number of prostate cancer patients have small, slowly growing cancers that probably won't be problematic in the next 10-15 years. Aggressive treatment with radical prostatectomy (RP) or radiation therapy (RT) has no proven benefit for these men. So, for every patient saved by prostate cancer screening, other men will be harmed by treatment they do not need. The best solution to this is to only treat men with cancers that pose a significant risk to their health.

We now have access to a rather extensive literature to aid us in identifying "clinically significant" cancer. I would recommend all newly diagnosed patients visit the AUA website and review the "AUA Guidelines for Clinically Localized Prostate Cancer" at <www.auanet.org/content/homepage/homepage.cfm>. This document clearly defines men with low-risk disease characteristics who can safely forego aggressive treatment and follow a "watchful waiting" or "active surveillance" approach (See Table 1).

(Continued on page 3)

Table 1. Some Characteristics of Candidates for Active Surveillance
Serum PSA level that is less than or equal to 10 ng/mL
Gleason score that is 6 or below
Cancer less than 1 cm in diameter that is confined to 1 side of the gland
Cancer does not threaten to invade the capsule surrounding the prostate gland

INSIGHT INTO THE NEED FOR BETTER RISK ASSESSMENT FOR MEN NEWLY DIAGNOSED WITH PROSTATE CANCER

Recently we had a chance to speak with Robert Shovlin, President and Chief Executive Officer of Aureon Laboratories, the developer of Prostate Px ⊕, a commercially available prognostic test for prostate cancer.

Why did Aureon choose prostate cancer for their first test?

Prostate cancer was an obvious choice for us for two reasons. First, so many men and their families are affected by prostate cancer, and the incidence of the disease is expected to increase as the population ages. Second, newly diagnosed men face a bewildering array of choices and many, sometimes conflicting opinions. This is an area where patients need as much information as possible to make informed treatment decisions. We believe that our information provides a unique, useful perspective to these patients.

How does the test work?

Each patient's biopsy sample (from the original biopsy) is sent to our central laboratory. Once at Aureon, the tissue is examined by our patented Systems Pathology approach. Cellular features as well as proteins involved in the disease process are integrated by mathematical tools to provide estimates for personalized patient outcomes. (See Case Studies on page 4).

How does your test fit into the debate over the benefits of PSA screening?

Annual PSA screening has allowed the detection of prostate cancer much earlier in the disease process. The problem is how to differentiate between the less aggressive and highly aggressive cancer cases. Our test is a risk stratification tool and is the first commercial test to address this question. Advanced molecular and computer analysis provides personalized outcome predictions that are a natural addendum to the screening discussion.

Why do you believe a molecular prognostic test is beneficial?

Many believe that PSA screening has resulted in an over diagnosis of prostate cancer that would otherwise be clinically insignificant had they not been detected. Risk assessments using standard clinical/pathological features

Aureon Laboratories CEO Robert Shovlin

such as PSA and Gleason score cannot reliably determine which cancers are truly low-risk versus those that are at a high-risk for progression. Today, the overwhelming majority of patients have Gleason scores of 6 or 7 and have PSA values below 20 ng/mL. The question really becomes, if all of the clinical and pathological features are trending within this more narrow range of lower risk, how do you identify the potentially high risk cases? We believe that this is exactly where our test has the most utility today.

Is this a genetic test?

No. This test does not look at a genetic signature. However, the test does examine proteins which are produced by the prostate cancer to support its growth. We believe this is vitally important because proteins represent the final product of the gene and impact upon many tumor promoting properties that are responsible for tumor cells traveling outside the prostate.

What information does the Prostate Px ⊕ test provide?

The test provides two endpoints. The first endpoint is 'Disease Progression' which predicts patients with the most serious disease outcomes, including metastasis, death from the cancer or PSA progression through androgen deprivation therapy post surgery. These predictions are provided in the form of a score on a scale from 1 to 100; the higher the number, the more at risk the patient is for this outcome.

The second endpoint is 'Favorable Pathology' which predicts from biopsy tissue what a patient's disease is like in the prostate if it were removed. This is important because the biopsy Gleason score is often upgraded (increased) after the prostate is removed and examined. Tools that provide improved confidence in the pathology at biopsy are important during treatment considerations. Think of the Favorable Pathology endpoint as if the surgeon could reach in and take out the prostate then examine it before actually doing surgery.

Why is this test better than current risk assessment methods?

Current risk assessment methods such as AUA risk categories or online calculators rely on clinical and pathologic information which has become less informative. Our approach uses the patient's own clinical data but also looks at the cellular organization of the biopsy tissue and various biomarkers associated with prostate cancer. It is this additional set of features that enables the test to provide a deeper layer of information for the individual patient.

What would I and my physician do with the information?

There is no one answer to this question. It depends on many variables about a patient's condition, treatment goals, existing health and how the treating physician wishes to proceed. What the test does do is provide objective information, not available from any other source, which allows one to make a more-informed decision about the path forward. Patients no longer have to fit into broad risk categories nor rely solely on existing information; more informed decisions can be made with a better understanding of each patient's unique situation.

Can I use this test to decide to have active surveillance?

At this time, we don't make a claim about active surveillance. This is because everyone in our study had surgery. We do say that the test can be used as a supportive tool to individually assess active surveillance candidates for prostate cancer progression. Also, we have physicians that use the test to further evaluate patients they already consider active surveillance candidates based on their clinical and pathological features.

(Continued on page 4)

UNDERSTANDING CANCER STAGE AND GLEASON SCORE

Cancer stage

Knowing the stage of your cancer provides important information for you and your care team as you explore your treatment options. There are treatment options that are specific to the various stages of the disease, whether it is caught early, at the advanced stages of cancer, or somewhere in between.

Stage I (T1) and stage II (T2) cancers are found only in the prostate. T1 cancers are small enough that you doctor is unable to feel it during your DRE. T2 cancers are larger and can be felt as firmness or a lump on a DRE.

Stage III (T3) and stage IV (T4) cancers are no longer confined to the prostate gland. T3 cancers have spread to nearby tissues but still remain inside the pelvic area. T4 tumors deeply invade surrounding tissues and may have metastasized to lymph nodes or bone.

Gleason Score

Your Gleason score helps your physician determine the best type of treatment for your particular cancer. The Gleason score describes different types of prostate cells and classifies tumors according to their microscopic appearance. The score helps to estimate of the rate your cancer might grow and your life expectancy. The lower your Gleason score is, the better your prognosis is likely to be.

The Gleason score is made up of two numbers (grades) that are determined by a pathologist and then added together. The first number indicates the grade of cancer cells that are most numerous in the biopsy sample. The second number indicates the grade of the cancer cells that are second most numerous. The Gleason score (sum) is determined by adding the primary and secondary grade patterns for each cancerous lesion found. e.g., 3 + 4 = 7.

Cancers having Gleason score of 2, 3 or 4 are considered non-aggressive whereas cancers that are 5 or 6 are considered mildly aggressive. Gleason 7 cancers are considered moderately aggressive while Gleason 8, 9 or 10 cancer are considered very aggressive.

For more useful information, refer to Us TOO's Signposts and Pathways brochures at <www.ustoo.org>.

THE PROSTATE CANCER SCREENING CONTROVERSY

(Continued from page 1)

These factors are associated with cancers that grow slowly, if at all. However, your general health is also an important consideration. If you have heart disease, diabetes, or other diseases likely to kill you within ten years, it is very unlikely that a low-risk cancer will effect your survival or quality of life. In contrast, if you are under 60 years of age and in excellent health, you may well have an excellent chance of being alive and well at age 80. In that case, even a low-risk cancer will have enough time to cause problems. For this reason, it is important to meet with your family physician for a frank assessment of your lifespan.

If your prostate cancer fits these low-risk criteria, you have several options. The watchful waiting approach involves no treatment. The patient is only periodically monitored for evidence of aggression. This involves a PSA determination every 3 months. Additionally, most investigators monitor the size and location of the cancer every 6-18 months. (See Table 2 for monitoring tools). In our clinic, we have found saturation biopsies the most accurate assessment tool for determining the extent and location of the cancer at diagnosis. However, it is too traumatic to be used for consistent monitoring. Color Doppler ultrasound is nearly as useful but much less traumatic for monitoring the cancer over time.

Table 2. Methods for determining cancer size and location
Transrectal ultrasound
Color Doppler ultrasound
Saturation biopsy
Endorectal MRI

During watchful waiting, two processes can cause the cancer to become more dangerous. First, the existing cancer can change over time to become more aggressive. Second, a new and more dangerous cancer can arise. Over the past few years, research has uncovered a range of agents to address this:

- Both Proscar® (finasteride) and Avodart® (dutasteride) have been shown to decrease prostate cancer risk in large, well-designed clinical trials
- There is strong epidemiologic evidence that vitamin D deficiency also increases the risk of prostate cancer (so increasing vitamin D consumption just makes common sense)
- Pomegranate had a dramatic impact on prostate cancer progression in a well-designed Phase II trial. A randomized controlled trial is underway

The Mediterranean diet has been shown to reduce the risk of heart disease, diabetes, and many cancers. In population studies, it is associated with a lower incidence of prostate cancer. Various investigators are looking at the addition of these and other agents to advance the watchful waiting process. This combined approach is now called active surveillance – and offers the chance to improve patients' general health while lowering cancer risk.

While clinical studies might create questions, I am happy to provide any answers you might have on this or any other subject. I invite all who read this to submit their questions to me either through Us TOO or through the FCRE website <www.prostateforum.com> and I'll be happy to answer them.

Reference

1. *Schröeder FH, Hogosson J, Roobol MJ, et al. N Engl J Med 360: 1320, 2009.*

INTRODUCTION

(Continued from page 1)

Us TOO International Prostate Cancer Education and Support Network works to support, educate and advocate for men with prostate cancer and their families.

"Our mission and program goal is to educate and empower men and their family members so men and their loved ones can take an active role in their healthcare," said Thomas Kirk, President and CEO of Us TOO International, Inc., which is based in Downers Grove, IL.

We sincerely hope that the information provided by this Burning Issues Supplement meets our goals and your needs.

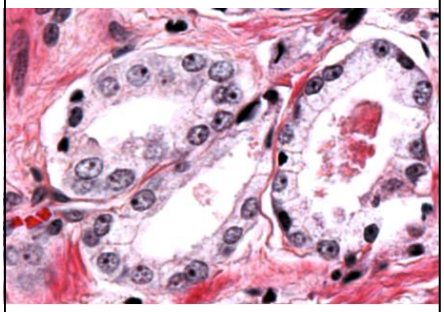
AUREON'S "SYSTEMS PATHOLOGY" APPROACH

Systems Pathology is an approach to combining different types of information to provide personalized cancer-focused, risk assessments for patients and their physicians. Each person's cancer is different and changes on the molecular level are not evident through existing, light-based microscopy. Systems Pathology assesses each individual's cancer by examining the tumor in the biopsy tissue. Using advanced mathematics, the approach objectively analyzes the information unique to the cells and specific molecules in each case. Systems Pathology combines clinical information with:

Image Analysis

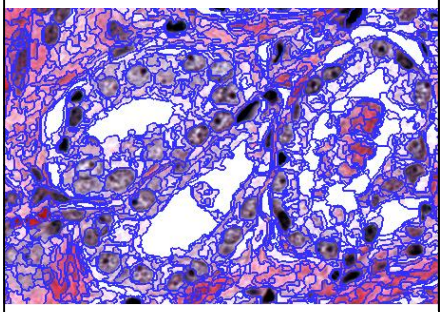
A digital image of each patient's biopsy tissue is analyzed by a special image system (Machine Vision) that uses technology to identify and measure hundreds of properties of the tumor.

Figure 1(A): *Original tissue image*



This image displays how biopsy tissue looks when stained with routinely used dyes and viewed by a pathologist.

Figure 1(B): *Machine vision image*

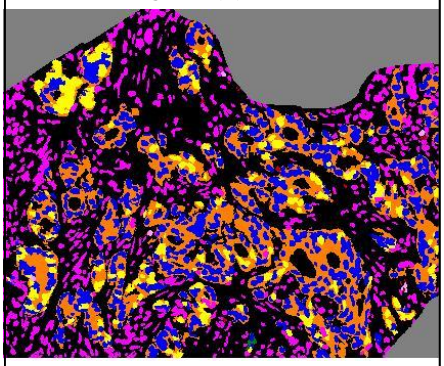


Aureon's approach locates, identifies and measures all of the cells and their relationships to one another in the tissue.

Molecule Detection

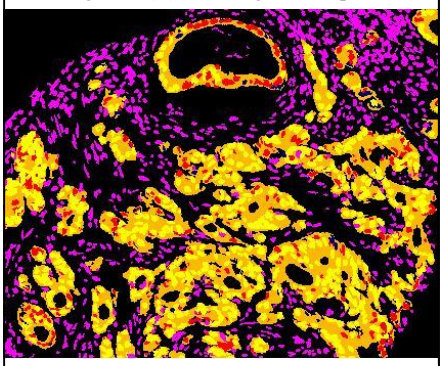
Eight proteins involved in tissue structure and function are located, measured and analyzed by an advanced fluorescence detection system. The two examples below demonstrate co-localization of multiple protein markers in the same tissue section.

Figure 2(A): *Ki-67*



The yellow sites in the tissue are positive for Ki-67, a protein associated with cell proliferation.

Figure 2(B): *Androgen Receptor*



The yellow sites in the tissue are positive for Androgen Receptor, a protein associated with prostate cancer progression.

Advanced Mathematics

Similar to artificial intelligence, advanced mathematics enables computers to learn, recognize patterns and make decisions. It is being applied in many fields such as bioinformatics, Internet search engines and stock market analysis. Aureon's approach can model prostate cancer data and improve upon the existing ability to provide an accurate prediction for patients.

PROSTATE PX⊕

(Continued from page 2)

How many patients were in the study that supports this test?

We had a very large, multi-institutional cohort. There were 1,487 patients and associated data from multiple physicians practicing at The Mayo Clinic, Duke University Medical Center/ Durham Veterans Administration, The University of Graz in Austria, University Hospital at Uppsala in Sweden and The University of Connecticut. After review, there were 1,027 evaluable cases in the cohort.

Is this test FDA approved?

Prostate Px⊕ does not require FDA approval. The test is considered a Laboratory Developed Test (LDT) and is performed in Aureon's state-of-the-art, CLIA-certified, CAP-accredited, New York State-regulated laboratory.

How long has the test been available?

The Prostate Px⊕ test was launched in June 2008.

CASE STUDIES

Case #1 was a 73 year old male with a negative DRE, and a high PSA of 16.3 ng/mL. He had clinical stage T1c disease and a biopsy Gleason score of 6.

AUA categorized him as intermediate risk. Calculators or nomograms available on the Internet considered him low risk but the Systems Pathology approach considered him at high risk because of his score of 39.

Actual Result

The patient experienced disease progression in 60 months.

Case #2 was a 59 year old man with a suspicious DRE, a PSA of 5.0 ng/mL and clinical stage T3 disease according to imaging studies. His biopsy Gleason score was 6.

AUA categorized him as a high risk patient. Calculators or nomograms available on the Internet considered him at a low risk and the Systems Pathology approach also considered him at low risk because of his score of 12.

Actual Result

The patient had no disease progression after fourteen years of follow-up.