AR-V7 mRNA May Predict Castration-Resistant Prostate Cancer Outcomes

“Androgen receptor (AR) splice variant-7 (AR-V7) present in circulating tumor cells (CTCs) strongly predicted outcomes in men with castration-resistant prostate cancer (CRPC) receiving novel hormonal drugs,” researchers said. “AR-V7 is an abnormally spliced messenger ribonucloic acid (mRNA) isoform of AR. Despite its inability to bind ligand, it remains active and can drive CRPC growth,” according to Emmanuel Antonarakis, MBCh, of the Johns Hopkins University School of Medicine in Baltimore, MD.

“Median progression-free survival (PFS) was three months in men with detectable AR-V7 in CTCs, compared with eight months for men without AR-V7 in these cells, and 14 months for men with no CTCs at all (P <0.001 for comparison),” the authors wrote online in the Journal of Clinical Oncology. Investigators were able to place patients in three prognostic categories based on AR-V7 test results: men without CTCs (CTC-) fared best, men with these cells but no AR-V7 (CTC+/AR-V7-) were intermediate, and men with both (CTC+/AR-V7+) fared worst. CTC+/AR-V7+ patients were more likely to have Gleason scores ≥8, metastatic disease at diagnosis, higher PSA and alkaline phosphatase levels, prior abiraterone or enzalutamide use, prior taxane use, presence of pain, and Eastern Cooperative Oncology Group (ECOG) performance status ≥2.

(Continued on page 4)

Black Men Should be Screened Earlier for Prostate Cancer

Compared with white men, black men develop preclinical prostate cancer at an earlier age and face a higher risk of metastatic progression, researchers report.

Prostate cancer incidence is 60% higher among black men than white men, and black men are more than twice as likely to die from it. Several studies have explored the likely drivers of these racial disparities without reaching definitive conclusions.

Dr. Etzioni and colleagues used prostate cancer incidence trends in the Surveillance, Epidemiology, and End Results (SEER) program to investigate and explain the differences in the natural history of prostate cancer in black and white men. Relative to the general population, black men were less likely to receive at least one PSA test in all but the youngest age groups, with the greatest disparities in PSA testing in the oldest age groups.

Based on the results of three natural history models, the risk of developing preclinical disease is 24% to 29% in the general population. Among black men, the risks rise to 30% to 43% (28% to 56% higher than those of the general population). Similarly, the risks of clinical diagnosis are 33% to 70% higher in black men than in the general population, according to the April 24th report published online in Cancer.

“Black men are not an average-risk population when it comes to prostate cancer and they should be recognized as such,” Dr. Ruth Etzioni from Fred Hutchinson Cancer Research Center in Seattle, Washington, told U.S. News.

(Continued on page 5)
Risks of Serious Toxicities from Intermittent vs. Continuous Androgen Deprivation Therapy for Advanced Prostate Cancer: A Population-Based Study

Tsai H-T, Pfeiffer RM, Philips GK, et al.

J Urol 2017: 197: 1251-1257

Purpose: Randomized trials have shown that intermittent androgen deprivation therapy (IADT) for men with advanced prostate cancer may improve sexual and physical functioning compared to continuous androgen deprivation therapy (CADT) without compromising survival. To our knowledge it is unknown whether IADT alters the risk of serious toxicities associated with CADT.

Materials and Methods: We performed a population-based cohort study of 9,772 men 66 years old or older who were diagnosed with advanced prostate cancer from 2002 to 2011 and treated with androgen deprivation therapy (ADT). IADT was defined as a single 90-day interval between two ADT sessions during which patients visited their physicians or underwent PSA testing. Outcomes included acute myocardial infarction, stroke, heart failure, type 2 diabetes and fracture. We used Cox proportional hazard models to estimate the hazard ratios (HRs) of the comparative risk of serious toxicities between IADT and CADT.

Results: A total of 2,113 (22%), 769 (9%) and 899 men (9%) had a new cardiovascular event, diabetes or fracture, respectively, within five years of starting ADT. Compared to the CADT group, the IADT group was at lower risk for serious cardiovascular events (HR 0.64, 95% confidence interval [CI] 0.53-0.77), particularly in reducing the risk of heart failure (HR 0.62, 95% CI 0.49-0.78) and fracture (HR 0.52, 95% CI 0.38-0.70, each p <0.0001).

Conclusions: IADT was associated with a lower risk of heart failure and fracture compared to CADT. This raises toxicity concerns for continuous (relative to intermittent) therapy and suggests that IADT may represent a safer therapeutic choice in elderly men with advanced prostate cancer.

PSA Testing Rates Appear to Level Off After Recent Drop

Declines in PSA testing that came after changes in government screening guidelines have abated in recent years, according to a new study. In JAMA Internal Medicine, American Cancer Society (ACS) investigators led by Stacy A. Fedewa, PhD, wrote that about one in three men aged 50 years or older still receive routine PSA testing.

Recommendations for PSA-based prostate cancer screening have changed considerably in recent years. In 2008, the U.S. Preventive Services Task Force (USPSTF) recommended against PSA-based prostate cancer screening among men aged 75 years or older, and in 2012, the group recommended against PSA testing for men of all ages. Other organizations, including the ACS, emphasize shared decision-making for men 50 years or older who have a long life expectancy.

In a previous ACS study, investigators showed shifting recommendations led to a decline in PSA screening rates that dropped from 37.8% in 2010 to 30.8% in 2013 among men 50 years or older, resulting in substantial declines in prostate cancer incidence.

To find out if the trend has continued, ACS researchers used recently released data from the 2015 National Health Interview Survey (NHIS) to examine testing patterns. They reviewed responses from 16,196 men over 50, more than half of whom were 50 to 64 years old. Three-quarters of the men had visited their primary care physician in the past year. They found that among men 50 years or older, rates of PSA testing for routine reasons in the past year remained stable at 32.1%.

“Physicians interested in adopting PSA testing may have done so, closely following the USPSTF recommendations and the media attention that came with it,” wrote the authors. They add that other physicians may be choosing to continue to offer PSA testing based on their beliefs about screening and interpretation of clinical trial results, as well as recommendations from other public health organizations that still support PSA testing, albeit with shared decision-making.

The authors pointed to a recent study that reported a modest short-term increase in the incidence of metastatic prostate cancer among men aged 75 years or older, but said continued evaluation is needed to determine how testing patterns influence prostate cancer outcomes over the long term.

Content in this post has not been reviewed by the American Society of Clinical Oncology, Inc. (ASCO®) and does not necessarily reflect the ideas and opinions of ASCO.

The ASCO Post 1 May 2017
Doc Moyad’s What Works & What is Worthless Column, Also Known As “No Bogus Science” Column

“Aspirin Is Having a Heck of a Good Year!”

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

Editor’s Note: Us TOO invites certain physicians and others to provide information and commentary for the Hot SHEET to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

One of the longest studies of aspirin, which was actually completed in Physicians’ Health Study (PHS), just found a lower risk of lethal prostate cancer, and another recent study in African American men just found a similar result.12 “Hey, Dr. Moyad you were right, HEART HEALTHY = PROSTATE HEALTHY = COLON HEALTHY!”

Oh man I love being right! It is really fun! And, I hate being wrong, for example when I said Michigan would beat Ohio State in football in 2016 and then they got robbed… um, I mean they lost to Ohio State. So, I have been using the words “Heart Healthy = Prostate Healthy” since the late 1990s. And, now it seems the most promising over the counter (aka OTC) agent to fight prostate cancer along with conventional treatment. It is not a supplement, but rather that thing that can prevent heart attacks and strokes. Aspirin gets a ton of attention for the prevention of colorectal cancer, but arguably the data in prostate cancer is beginning to compete with colorectal cancer data. For example, Physicians’ Health Study is one of the most famous clinical trials of aspirin to prevent heart attacks and included over 22,000 docs (started in 1981), but these brilliant Harvard folks/researchers have continued to follow this group even when the trial ended. They just found in 2017 that current aspirin use was associated with a lower risk of “lethal” prostate cancer (defined by researchers as metastases or prostate cancer death) and even death from all causes! The reason this is so darn compelling is it is one of the longer looks at people taking aspirin and suggests that taking it after a diagnosis of prostate cancer could slow the progression of this disease.

WOW! And, if that was not enough to make your day, then a much-needed study of African American men done in the U.S. essentially found the same result! This is awesome! Of course I can use the politically correct sentence that so many “experts” love to use right now, which is: “We need a randomized trial to see if these results are true before we start recommending aspirin.” Blah! BORING!! What we need is for you to work with your doctors including your primary care doctor and your urologist/oncologist to see if you QUALIFY for aspirin based on your cardiovascular risk and, if you do, then you may get a 2 for 1! And, go to www.cvriskscalculator.com (mentioned before by Moyad in other articles - you just need to type in your age, gender, race, total cholesterol, HDL cholesterol, blood pressure information and whether you are diabetic or a smoker = 20 SECONDS OF YOUR TIME) and see if you may qualify for aspirin, and then print your result and share it with your doctors you love and trust to make a final decision that is best for YOU! If you do qualify, then baby aspirin also appears to have good results with less toxicity versus regular adult aspirin. But your dose should be decided by you and the docs around you, and not by some bitter doctor that writes a column for Us TOO that still thinks we got robbed by referees … ummm, I mean that still thinks we should have beaten Ohio State in football last year! Oh, and if aspirin is not found to reduce the risk of aggressive prostate cancer many years or decades from now, I apologize that all it may have done for you was reduce your risk of colorectal cancer, and/or a heart attack, and/or a stroke, blah blah blah … I think you just caught the Moyad sarcasm train! ALL ABOARD!

References:

Predicting Metastatic Disease After Radical Prostatectomy

An individual patient-level meta-analysis has shown that the Decipher® (GenomeDx) genomic classifier is capable of distinguishing risk groups for metastatic disease after radical prostatectomy (RP) for prostate cancer. The study was reported by Spratt and colleagues in the Journal of Clinical Oncology.

The analysis included five studies published between 2011 and 2016 that assessed performance of the Decipher test. Of the total of 975 men, 855 had available individual patient-level data. Multivariable Cox proportional hazards models fit to individual patient data were performed; meta-analyses were performed by pooling the study-specific hazard ratios (HRs) using random-effects modeling. Decipher provides a continuous score between 0 and 1, with higher scores indicating a greater risk of metastasis. Cutpoints of 0.45 and 0.60 are used to categorize men into low-, intermediate-, and high-risk groups.

Median follow-up for all patients was eight years. In the cohort of 855 men, 60.9%, 22.6%, and 16.5% were classified by Decipher as low-, intermediate-, and high-risk, respectively. The five-year cumulative rates of metastases were 2.4%, 5.8%, and 15.2% in these risk groups, and the 10-year cumulative rates were 5.5%, 15.0%, and 26.7% (P <0.001). Pooling of the study-specific HRs across the 975 men in the five studies resulted in a HR of 1.52 per 0.1 Decipher unit increase (95% confidence interval [CI] =1.39-1.67; I2 test for heterogeneity = 0%).

On multivariable analysis of individual patient data including preoperative PSA level, RP Gleason score, margin status, extracapsular extension, seminal vesicle invasion, and lymph node invasion, Decipher remained a significant predictor of metastasis (HR = 1.30, P <0.001, per 0.1 unit). The C-index for 10-year distant metastasis was 0.76 for the clinical model alone and increased to 0.81 (Continued on page 6)
AR-V7 mRNA & CRPC (Continued from page 1)

Group performance status ≥1, the study found. Outcomes were better in men receiving novel hormonal therapy – abiraterone or enzalutamide for the first time, compared with men who had received one of these drugs previously.

In patients receiving first-line therapy, median PFS was four months in CTC+/AR-V7+ men, 10 months in CTC+/AR-V7- men, and 22 months in CTC- men. For those receiving second-line therapy, PFS was three months in CTC+/AR-V7+ men, five months in CTC+/AR-V7- men, and six months in CTC- men (P <0.001 for all comparisons).

“The study expanded on a previous study that excluded men without CTCs,” Antonarakis told MedPage Today. “We wanted to create a biomarker that would have meaningful prognostics for all CRPC patients, not just those with CTCs.”

“We are very close to using this biomarker to make clinical decisions. In patients with CTCs that express AR-V7, novel hormonal therapy is ineffective. These patients should receive other treatments, such as chemotherapy, instead of novel hormonal therapy,” he said.

“This is a well-designed study that adds to our current knowledge base, which suggests that CTC presence has a prognostic role in advanced prostate cancer,” said Sunmanta Kumar Pal, MD, of the City of Hope in Duarte, CA, and a spokesperson for the American Society of Clinical Oncology (ASCO), who was not involved in the study.

“The data provided herein suggest an additional prognostic role of AR-V7 status—adding this to CTC presence/absence yields powerful information regarding prostate cancer aggressiveness.”

The study prospectively enrolled 202 men with metastatic CRPC starting abiraterone or enzalutamide. Patients had to have histologically confirmed prostate adenocarcinoma, progressive disease despite a castrate testosterone (<50 ng/dL), and metastases on computed tomography (CT) or technetium-99 (99mTc) bone scans.

Patients underwent PSA measurements every one to two months, as well as CT (chest, abdomen, and pelvis) and 99mTc bone scans every two to four months. The primary study outcome was clinical and radiographic PFS. Median follow-up ranged from 15 to 22 months.

The investigators used a modified AdnaTest platform to detect AR-V7. They designed custom primers to detect full-length AR mRNA and AR-V7 mRNA. Overall, 53/202 (26.2%) men were CTC-negative, 113 (56.0%) were CTC+/AR-V7-, and 36 (17.8%) were CTC+/AR-V7+.

One study limitation was that it only included men treated with novel hormonal therapy and not other treatments, such as chemotherapy. “The predictive usefulness of this biomarker and the interaction between biomarker status and treatment type could not be evaluated and will form the basis of future work,” investigators said.

“This expanded analysis confirms the negative prognostic impact of CTC-based AR-V7 detection in men with CRPC undergoing abiraterone and enzalutamide therapy and suggests that this biomarker panel may be useful in the prediction of response to first- and second-line AR-targeted treatment with novel hormonal therapy settings,” they said.

MedPage Today 18 April 2017

A Pilot Study of a Multimodal Treatment Paradigm to Accelerate Drug Evaluations in Early-stage Metastatic Prostate Cancer


Objective: To evaluate a multimodal strategy aimed at treating all sites of disease that provides a rapid readout of success or failure in men presenting with non-castrate metastatic prostate cancers that are incurable with single modality therapy.

Materials and Methods: Twenty selected men with oligometastatic M1a (extrapelvic nodal disease) or M1b (bone disease) at diagnosis were treated using a multimodal approach that included androgen deprivation therapy (ADT), radical prostatectomy (RP), plus pelvic lymphadenectomy (retroperitoneal lymphadenectomy in the presence of clinically-positive retroperitoneal nodes), and stereotactic body radiotherapy (RT) to osseous disease or the primary site. Outcomes of each treatment were assessed sequentially. ADT was discontinued in responding patients. The primary end point was an undetectable PSA after testosterone recovery. The goal was to eliminate all detectable disease.

Results: Each treatment modality contributed to the outcome: 95% of the cohort (Continued on page 8)

Second-Line Hormonal Therapy (Continued from page 1)

continue treatment to maintain castrate levels indefinitely.

- Second-line treatment with abiraterone plus prednisone or enzalutamide is recommended for men with radiographic evidence of metastatic progression (M1a/M1s), as both agents demonstrated ability to improve progression-free survival and overall survival.

- Palliative care should be offered with second-line hormonal therapy.

- Men with low-risk nonmetastatic CRPC should have a PSA assessed every four to six months, decreasing to three-month intervals for men with high-risk nonmetastatic disease or existing metastases.

- Radiographic monitoring should consist of a bone scan and either CT scan or MRI of the abdomen and pelvis; with frequency of follow-up imaging guided primarily by symptoms.

- Radiographic monitoring is not recommended for men with CRPC and rising PSA level, unless imaging would affect treatment decisions or symptoms suggest disease worsening.

- Routine radiographic re-staging is not indicated except for patients in whom PSA is not a reliable marker of disease status.

A panel of experts developed the PCO on the basis of a literature review covering 1985 through October 2016, consensus opinion, and clinical experience.

“We hope that this PCO will offer clinicians and patients timely direction to help inform treatment planning and shared decision making,” said Panel Co-Chair Eric A. Singer, MD, of Rutgers Cancer Institute of New Jersey in New Brunswick.

MedPage Today 25 April 2017
Black Men Should be Screened Earlier
(Continued from page 1)

Seattle told Reuters by email. “Guidelines for the general population do not apply to them. It is important for black men to be well informed about the potential benefits and risks of prostate cancer screening so that they can make a decision that is right for them. It is appropriate for this to happen at an earlier age than is recommended for the general population.”

Among men who already have preclinical disease, the risk of clinical diagnosis is similar for blacks and all races, and this translates into times from disease onset to diagnosis that are very similar for black men and for the general population. Black men, however, are 44% to 75% more likely than the general population to develop metastasis before diagnosis.

“The model results consistently demonstrated that the risk of onset of a preclinical prostate cancer explains a majority of the observed incidence disparities,” the researchers note. “On the basis of these results, we conclude that black men have more preclinical and progressive prostate cancer than men in the general population. They are more likely to develop prostate cancer at a younger age, and they are more likely to progress to a metastatic state and/or higher grade before clinical diagnosis.”

“We have not figured the exact most preferred approach for black men,” Dr. Etzioni added, “but if the U.S. Preventive Services Task Force (USPSTF) is recommending that average-risk men start shared decision making about prostate cancer at age 55, then black men should be doing this at age 50 or between 45 and 50 if we agree that we want to provide black men the same opportunity to improve their chances (in terms of reducing the burden of disease) as we are providing to the average risk population.”

Dr. Lauren P. Wallner from the University of Michigan in Ann Arbor, who co-authored an editorial related to this report stated, “While the results of the study were not surprising, they are interesting and very timely because they inform the discussion about the appropriateness of having a ‘one size fits all’ approach to prostate cancer screening.”

She continued: “The findings that African American men are much more likely to progress to metastatic disease prior to diagnosis, when compared to the general population, suggest that early detection via screening may be particularly important in this group. However, studies directly evaluating the effectiveness of PSA screening in African American men are still lacking. Therefore, it remains unknown whether PSA screening offers African American men a greater benefit in terms of preventing mortality due to prostate cancer when compared to the general population.”

Dr. Firas Abdollah from Henry Ford Hospital and Vattikuti Urology Institute, Detroit, Michigan told Reuters Health by email, “Unfortunately, the currently available trials addressing the role of PSA screening have included a very limited number of black men and, as such, are not necessarily generalizable to this population. The issue of under-representing minorities is common to many clinical trials, and this should be avoided in future trials.”

Reuters Health
26 April 2017

Re-Examining Prostate-Specific Antigen (PSA) Density: Defining the Optimal PSA Range and Patients for Using PSA Density to Predict Prostate Cancer Using Extended Template Biopsy
Ju JS, Barboza MP, Prakash NS, et al.
Urology 18 April 2017, (Epub ahead of print)

Objective: To compare the predictive accuracy of PSA density (PSAD) vs. PSA across different PSA ranges and by prior biopsy status in a prospective cohort undergoing prostate biopsy.

Materials and Methods: Men from a prospective trial underwent an extended template biopsy to evaluate for prostate cancer at 26 sites throughout the United States. The area under the receiver operating curve (ROC) assessed the predictive accuracy of PSAD vs. PSA across three PSA ranges (<4 ng/mL, 4-10 ng/mL, >10 ng/mL). We also investigated the effect of varying the PSAD cutoffs on the detection of cancer and assessed the performance of PSAD vs. PSA in men with or without a prior negative biopsy.

Results: Among 1,290 patients, 585 (45%) and 284 (22%) men had prostate cancer and significant prostate cancer, respectively. PSAD performed better than PSA in detecting any prostate cancer within a PSA of 4-10 ng/mL (area under the ROC curve [AUC]: 0.70 vs. 0.53, P <0.001) and within a PSA >10 mg/mL (AUC: 0.84 vs. 0.65, P <0.001). PSAD was significantly more predictive than PSA in detecting any prostate cancer in men without (AUC: 0.73 vs. 0.67, P <0.001) and with (AUC: 0.69 vs. 0.55, P <0.001) a previous biopsy; however, the incremental difference in AUC was higher among men with a previous negative biopsy. Similar inferences were seen for significant cancer across all analyses.

Conclusion: As PSA increases, PSAD becomes a better marker for predicting prostate cancer compared with PSA alone. Additionally, PSAD performed better than PSA in men with a prior negative biopsy.

Structure-Based IsoPSA Assay Outperforms PSA Concentration for Prostate Cancer Diagnosis
Klein, EA, et al.
European Urology, 7 April 2017 Epub

A new structure-based IsoPSA serum assay outperforms assays of total PSA (tPSA) for predicting the overall risk of prostate cancer and the risk of clinically-significant disease, according to a preliminary report.

“Recognition of structural changes to PSA have better diagnostic accuracy than measurement of the PSA parent protein alone, but current assays relying on isoforms of PSA lack sensitivity,” researchers say.

Dr. Eric A. Klein from Cleveland Clinic, in Cleveland, OH, and colleagues evaluated the performance of IsoPSA, an assay that considers the entire spectrum of structural changes of the PSA complex, in a prospective study of 261 men referred for prostate biopsy on the basis of current clinical criteria.

Overall, 53.3% of men were diagnosed with prostate cancer (defined as a Gleason
**QIAGEN to Market Test That Shows if Prostate Cancer is Responding to Two Therapies**

QIAGEN will market a test that Johns Hopkins University (JHU) developed to detect if men with advanced castrate-resistant prostate cancer (CRPC) are failing to respond to the widely used therapies enzalutamide (Xtandi®) and abiraterone (Zytiga®).

If doctors know a patient is resistant to the drugs, they can develop a more tailored treatment. The test, called AdnaTest Prostate Cancer Panel AR-V7, will detect that resistance. If used, researchers can the test to help select patients for clinical trials.

Xtandi and Zytiga are hormone therapies for CRPC. They block the androgen receptor (AR) signaling that is essential to the cancer’s growth. Although they represent breakthroughs in metastatic CRPC treatment, 20 to 40 percent of patients fail to respond to them.

JHU researchers discovered that prostate cancer patients who lacked an AR variation known as AR-V7 survive longer than those with the variation. The study, “AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer,” was published in the *New England Journal of Medicine* in 2014.

The researchers also discovered that the variation was associated with resistance to Xtandi and Zytiga. The drugs failed to block AR signaling, allowing prostate cancer cells to keep growing.

Thirty-one men in the study received Zytiga and 31 Xtandi and results were clear. The PSA response rate was zero in men with the AR-V7 variant: In other words, none of the men responded to the drugs. In contrast, 54% of men who lacked the variant responded to Zytiga, and 68% responded to Xtandi.

Overall survival rates of patients with the variant were 5.5 and 10.6 months with Zytiga and Xtandi, respectively. Patients without the variation survived beyond the duration of the study.

The test is called a liquid biopsy, which can determine if cancer cells in a blood sample have the AR-V7 variation. “Our AdnaTest workflow unlocks an important biomarker for clinical research to provide for the development of prostate cancer diagnostics in the future. Providing accurate insights from circulating tumor cells in a blood sample, our AR-V7 solution is a significant addition to our portfolio of non-invasive liquid biopsies for personalized healthcare,” Thierry Bernard, a senior vice president of QIAGEN, said in a press release.

“We are pleased to partner with the pioneering researchers at Johns Hopkins in developing this workflow. We plan to make the AdnaTest kit commercially available this year, as a sample to insight solution for clinical researchers.”

*Prostate Cancer News Today* 20 April 2017

**Decipher® Test**

(Continued from page 3) when Decipher was included.

The investigators concluded: “The genomic classifier test, Decipher, can independently improve prognostication of patients post-prostatectomy, as well as within nearly all clinicopathologic, demographic, and treatment subgroups. Future study of how to best incorporate genomic testing in clinical decision-making and subsequent treatment recommendations is warranted.”

The study was funded by the Prostate Cancer Foundation Young Investigator Award. Felix Y. Feng, MD, of the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, is the corresponding author of this article.

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*The ASCO Post* 17 April 2017

**Structure-Based IsoPSA Assay** (Continued from page 5)

score of at least 6), including 33.7% with high-grade prostate cancer (defined as Gleason ≥7).

As measured by ROC (Receiver Operator Characteristic) curve, IsoPSA significantly outperformed tPSA for diagnosing prostate cancer (AUC, 0.79 vs. 0.61 for tPSA) and for diagnosing high-grade cancer (AUC 0.81 vs. 0.69 for tPSA).

Based on decision-curve analyses, the use of IsoPSA instead of tPSA would result in a 48% reduction in unneeded biopsies for diagnosing prostate cancer and a 45% reduction in unneeded biopsies for identifying men with high-grade prostate cancer.

“In conclusion, this study demonstrates, for the first time, that use of a structure-based rather than concentration-based assay of PSA has better diagnostic accuracy for detecting any cancer and high-grade cancer in a cohort of men undergoing biopsy for standard clinical indications,” the researchers write. “Once validated, use of Iso-PSA may substantially reduce the need for biopsy, and may thus lower the likelihood of overdiagnosis and overtreatment of nonfatal prostate cancer.”

Dr. Stacy Loeb from New York University, an expert on prostate cancer and its diagnosis, told Reuters Health by email, “IsoPSA needs further validation before it can be used in clinical decisions. If these results are confirmed in other studies, IsoPSA may eventually be used as a second-line test to help men decide on prostate biopsy.”

“Additional studies are needed to compare IsoPSA to other commercially available prostate cancer markers in this space,” said Dr. Loeb, who was not involved in the study.

“Future studies should also examine whether IsoPSA could be used in other scenarios, such as in patients who are already diagnosed with prostate cancer to help with management decisions.”

“This is an exciting time in prostate cancer research where we have many new options to offer patients,” Dr. Loeb added. “In the past, the traditional PSA test was used to make decisions about prostate biopsy, but it is not a perfect test, so many men underwent unnecessary biopsies or were diagnosed with prostate cancers that would not have caused harm. It is exciting to have several new markers that are better at identifying which men actually have aggressive prostate cancer and that can help patients to make better decisions about whether to have a prostate biopsy.”

Cleveland Diagnostics funded the study and employed several authors of the report.

*Reuters Health* 25 April 2017
Doctor Chodak’s Bottom Line


**Editor’s Note:** Us TOO has invited certain physicians and others to provide information and commentary for the Hot SHEET to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

**P1, “First Guide to…”** The improvements in second line hormonal therapy for men with CRPC prior to chemotherapy have created a new challenge in terms of what to do and when to do it. A new guideline from the American Society of Clinical Oncology may help men faced with this condition. Among the important recommendations, they state that abiraterone plus prednisone or enzalutamide are appropriate choices providing there is radiographic evidence of metastatic disease progression. Unfortunately, the ASCO panel did not provide any additional guidance about which of those choices to use first. Several studies, including the report in this Hot SHEET by Antonarakis et al. ([P1, AR-V7 mRNA Helps...](#)) have found that men with androgen receptor splice variant 7 (AR-V7) in circulating tumor cells had a very poor response to either of these drugs. Other reports demonstrated that regardless of the AR-V7 status, men did respond to taxane chemotherapy. Perhaps more work is needed to fully establish testing for AR-V7 before they recommend it, although QIAGEN is working on a commercial test to make this determination. A surprising recommendation from ASCO is to not do radiographic studies for a rising PSA unless it will lead to a change in therapy. If new bone lesions are identified, even in the absence of symptoms, treatment may be indicated to prevent fractures. A better guideline would have been to state the increase in PSA that is needed before doing one of these studies.

**The Bottom Line:** New ASCO guidelines for managing CRPC provide some helpful information for doctors.

**P1, “Black Men Should…”** Recently, the USPSTF has issued a preliminary update to its recommendations regarding screening for prostate cancer and changed the level from D (against screening) to C (discuss the pros and cons and let the patient decide). In their statement, the USPSTF acknowledged the higher risk among African American men but could not make a different recommendation because it cannot be supported by any real data. They did, however, acknowledge that decision models provide support for screening these men at an earlier age than 55, in part based on the studies from Etzioni et al. that are also described in this Hot SHEET.

The problem is that having a higher risk does not clearly translate into having a greater benefit from screening starting before age 55. For that reason, clinicians will have to be very careful in how they counsel this group of men. Making them aware of the higher risk is clearly important but it must be accompanied by a clear acknowledgement of the uncertainty of starting screening at age 50 and the greater risk of being diagnosed with a non-life-threatening cancer that is likely to get treated.

**The Bottom Line:** In the absence of clear data on screening African American men before age 55, clinicians must be very careful in the way they counsel these men before ordering a PSA.

**P2, “Risk of Serious…”** Previous studies have evaluated the difference between intermittent (IAD) and continuous androgen deprivation (CAD) on some quality of life effects. Patients were better off on IAD for sexual drive and sexual function. In a new cohort study by Tsai and co-workers involving nearly 10,000 men, they found a significantly lower incidence of heart failure and fracture for men on IAD compared to CAD. This presents a challenge for patients because IAD results in a lower survival compared to CAD for men with metastatic disease. For those without metastatic disease, cancer-related survival was similar in both groups, so now there are additional reasons to use it.

**The Bottom Line:** Men on IAD have a lower incidence of heart failure and fracture compared to men on CAD.

**P2, “PSA Testing Rates…”** The 2012 report from the USPSTF recommended against routine screening because they believed the risks outweighed the benefits. Apparently, that has had an effect on physician behavior as demonstrated in the report by Fedewa et al. They found that only about one-third of men have been getting PSA tests. Now that a new recommendation is forthcoming, one might expect the screening rate to increase, but that will depend, in part, on what information, if any, men are given by their primary MD. With the new recommendation that will occur, it is very important that men receive balanced information about the pros and cons so they can make their decision. This will be time consuming and challenging for the average doctor. As said before, I believe a standardized consent form could greatly aid both doctors and patients and hopefully that will occur.

**The Bottom Line:** Since the last USPSTF recommendation against screening, only about one-third of men have been screened for prostate cancer, however, that is likely to increase because of the new USPSTF guidelines that will soon be released.

**P3, “Predicting Metastatic…”** Despite potentially curative therapy, a proportion of men are at risk of developing metastatic disease at some time following definitive treatment. Identifying at-risk patients before that event would enable them to participate in clinical trials aimed at delaying or preventing those metastases from occurring. A paper by Feng and co-workers looked at the impact of using the Decipher genetic test in improving the ability to predict metastases. Although the prediction rate from adding this test was better, the overall improvement was only 5%. One of the shortcomings is that it does not deliver a yes or no answer. It simply provides a probability with higher risk associated with a higher score on the test. Given the cost and the low marginal value, one can reasonably question whether the test is worth doing.

**The Bottom Line:** Decipher for predicting prostate cancer metastases adds a small gain to the predictive ability compared to using clinical criteria alone. However, it is unclear whether this marginal gain has true clinical value.

**P4, “A Pilot Study of…”** O’Shaughnessy et al. present very preliminary data on a highly controversial approach.

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Doctor Chodak’s Bottom Line (continued from page 7)

approach to managing advanced prostate cancer that includes a radical prosta-
tomy (RP). Removing the primary tumor as part of a combined approach is not an unreasonable attempt to cure men of their disease. However, outside of a ran-
domized study, it will be impossible to assess the impact of that aspect of the com-
bined approach and whether it will make a difference in a man's survival. One could raise ethical concerns about continuing to accrue many more men outside of a proper clinical trial. Even in their small cohort, it will take many years to know the clinical course in these men, and even then, it will be impossible to know whether the RP contributed to those outcomes in a meaningful way.

The Bottom Line: Performing a RP in men with metastatic disease as part of a com-
prehensive treatment approach needs to be studied in a proper clinical trial to truly assess if it should play a role in patient management.

P5, “Re-Examining PSA...”

A new study by Ju et al. suggests that PSA density has a better ability to diagnose prostate cancer compared to PSA alone. They conducted a prospective study of nearly 1,300 men and found that PSA density was more accurate. The question is, what does this mean? One may question whether the information really matters. Since neither PSA nor PSA density can detect 100% of the cancers, a biopsy will always be necessary. Knowing the density before the biopsy may shift the odds that a cancer will be found, but a biopsy will still be performed.

The Bottom Line: Although PSA density has a higher positive predictive value for prostate cancer compared to PSA alone, knowing this information does not help with patient care.

P5, “Structure-Based...” Another prostate cancer detection report by Klein and associates compared IsoPSA to PSA and also found that it was better able to discriminate between cancer and benign disease. The authors conducted their assessment in 281 men and found that IsoPSA would be able to spare nearly half the men from having a biopsy, but it is unclear from this abstract how many men with high-risk cancer might be missed with this approach. More data are needed to determine its potential role in diagnosing this disease. However, discussion about using it either with, or in place of, PSA as a screening test would require a long-term prospective randomized trial. Without this study design, it is impossible to truly assess whether an IsoPSA test is a better tool for discriminating between prostate cancer and benign disease.

The Bottom Line: IsoPSA may enable many men to be spared from a biopsy, but its role in diagnosing this disease needs more data.

Multimodal Treatment (Continued from page 4)

achieved an undetectable PSA with multimodal treatment, including 25% of men after ADT alone and an additional 50% and 20% after surgery and RT, respectively. Overall, 20% of men (95% confidence interval: 3%-38%) achieved the primary end point, which persisted for five, six, 27+, and 46+ months. All men meeting the primary end point had been classified with M1b disease at presentation.

Conclusion: A sequentially applied multimodal treatment strategy can eliminate detectable disease in selected patients with metastatic spread at diagnosis. The end point of undetectable PSA after testosterone recovery should be considered when evaluating new approaches to rapidly set priorities for large-scale testing in early metastatic disease states and to shift the paradigm from palliation to cure.