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PCa Commentary

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THE VENERABLE PSA TEST: Sharpening Its Diagnostic Focus

To cure prostate cancer or control its progression it is necessary first to make a diagnosis. Without early awareness, the disease otherwise presents at a symptomatic incurable stage. Currently, the PSA test, properly applied, is the mainstay for identifying prostate cancers that benefit from early treatment or can be safely managed by active surveillance.

The recently FDA approved PHI test (Prostate Health Index) will soon join the PSA in this role.

Results of mature screening studies since the USPSTF 2012 recommendation of no screening:

There are positive European clinical trials and well reasoned arguments calling for modification of the USPSTF's dictum not to screen for prostate cancer. Since 2012 when the USPSTF issued its recommendation against *ALL* PSA screening, the clinical trial data and its analysis have matured. Heavy weight had been placed on the Prostate, Lung, Colorectal and Ovarian Trial in which the statistical foundation is considered compromised ("contaminated") because 52% of the enrolled subjects had been prescreened with PSA.

Three large European trials now have been reported at long follow-up. By the 12th year of follow-up, the European Randomized Screening for Prostate Cancer (ERSPC) found that the

- screened men compared to non-screened controls showed a 31% relative decrease in the development of metastatic disease and a
- 29% relative reduction in the risk of prostate cancer specific mortality (when adjusted for non-compliance).

In these studies only <15% of men had been pre-screened for PSA. At 12 years follow-up 70% of all men randomized are alive and analysis of 13-year follow-up data is ongoing.

The ERSPC cooperative trial was conducted at 8 centers and involved 182,160 men between ages 50 and 74. Screening in these trials was conducted at 4-year intervals, except for the Swedish arm with 2 year intervals. Men whose PSA exceeded 3 ng/ml underwent a prostate biopsy. The Rotterdam trial arm at 13 years reported a 51% relative reduction in mortality. The Goteborg trial found a 44% reduction at 14 years of follow-up. The results of these trials were summarized by Schroder in *Recent Results in Cancer Research.* 2014.

PSA Test continued:

Prostate cancer is most-times a slow moving disease and sufficient time is required for events to declare themselves, thereby conferring increased credibility to these ERSCP long follow-up results.

Many European thought leaders are convinced that the ERSPC trial results validate PSA screening and are now engaged in devising screening protocols to improve screening efficiency.

However, probably the most compelling argument for PSA testing is the widespread public intuitive sense that……

> When facing a disease that claims more than 30,000 lives yearly, it is inappropriate to pass up the opportunity for early diagnosis, potential cure, or control of the disease. Since the time of the "no screen" recommendation, studies have shown that prostate cancer is now presenting at a more advanced stage. As expressed by Dr. Scardino (JNCI, March 2014): "PSA testing is here to stay. The question is not whether we should screen but how best to screen to minimize harms and maximize benefits."

Honing the PSA's diagnostic accuracy for finding significant cancer, reducing the number of tests, and avoiding unproductive biopsies has now become the goal for many prostate cancer experts.

<u>Screening program recommendations based on risk stratification</u>:

The emerging proposals - especially in Europe, incorporate risk-stratified PSA screening protocols which recommend an appropriate interval for testing by incorporating data that project the future risk for the diagnosis of disease based on a man's age and baseline PSA level.

Studies have shown that a single baseline PSA of <1 ng/ml is highly predictive of the risk of developing significant prostate cancer later in life. CJ Weight with Mayo Clinic colleagues (*Urology. 2013 Oct 19)* found that with a follow-up of 16.3 years a man in the 40-49 yr range with a PSA value of <1 ng/ml had a 0.6% of being diagnosed with Gleason 6 prostate cancer by age 55. The risk was 15.7% for men with PSA values >1 ng/ml. "No man with a low baseline PSA developed intermediate or high-risk CaP, whereas 2.6% of men with a higher baseline PSA did."

[For reference, only the top 10% of men 45-49 have PSA values above 1.6 ng/ml and men above this level have increased risk (44%) for prostate cancer. The median PSA for ages 45-49 is 0.68 ng/ml; for age 51-55, 0.85 ng/ml.]

PSA Test continued:

An editorial comment by Dr.Catalona, Professor of Urology, Director of the Clinical Prostate Cancer Program, Northwestern University School of Medicine, speaks to testing of healthy men older than 70 years whose PSA values are >1 ng/ml : **"In regard to when to stop testing, it should be borne in mind that men over 70 years have a more aggressive disease (50% of prostate cancer deaths occur in men diagnosed over 75 years) and many would benefit from early diagnosis and treatment" [and continued testing]. He was referencing Messing, "Prostate Cancer in the Elderly."** ***Cancer*****. 15 June 2012."**

Another study (Carlsson S, BMJ. 2014 Mar) found that men with PSA <1 ng/ml at age 60 need no further testing; whereas a man with PSA >2 ng/ml benefits from further testing.

Dr. Timothy Wilt, Professor of Medicine, University of Minnesota, and Dr. Peter Scardino, Chief of Surgery MSKCC, have incorporated the principles of risk stratification into a set of recommendations: ("Prostate-Specific Antigen Screening in Prostate Cancer: Perspective on the Evidence," *J Natl Cancer Inst.* 2014).

- Age 45, PSA <1 ng/ml — screening every 5 years to age 50, 55, and 60; and if <1 ng/ml at age 60 no further testing;
- Age 45-69, PSA between 1 and 3 ng/ml — screening every 2 - 4 years;
- Age 70: for "previously screened men older that 70 years, in all men with short life expectancy (i.e. 10 – 15 year longevity), and men with serious comorbid conditions — no screening is recommended.

As in the ERSPC trial, they would consider a biopsy for men whose PSA >3 ng/ml "after an evaluation" that includes the PHI test (see below), the PCA3 urine test, or a gene-based biomarker panel.

Andrew Vickers, DPhil (MSKCC; specialist in the methodology of clinical research) came to a similar conclusion based on a risk stratification analysis: "Predicting prostate cancer many years before diagnosis: how and why?" (*World Journal of Urology*, 2011 Nov). His recommendations:

Age 45, PSA <1ng/ml — screening every 6 - 8 years;
Age 45-60, PSA >1 ng/ml — retesting every 2 - 4 years;
Age >60, PSA, "less than 1 or 2" — no further testing.

Another regimen of stratifying PSA testing frequency is being pursued by Randazzo *et al.* in *Eur Urol.* 2014 Apr)*:*

Their conclusion: "We observed men with a prostate-specific antigen (PSA) level of ≤3 ng/ml during 12 yr and found that men can be retested according to their initial PSA value ("PSA pyramid): PSA < 1 (base), retest interval every 8 years; PSA 1-2 (center), retest interval every 4 yr; and PSA 2-3 (top) retest yearly after risk stratification."

These three examples convey the general thrust of a screening policy based on an effort to match harms and benefits and tie screening recommendation to risk stratification based on age and PSA level. Indiscriminate yearly screening is clearly not recommended.

A Potential Game Changer —The Beckman-Coulter Prostate Health Index:

The calculations that have informed the vigorous debate about PSA screening are likely to change in the near future with the introduction of the Beckman/Coulter Prostate Health Index (PHI). This extensively validated test combines into a single number the results of three well-recognized tests: the PSA, the %free/total PSA, and the less recognized [-2]proPSA. The [-2]proPSA is an earlier form of PSA that is highly concentrated in prostate cancer tissue.

The PHI test has been FDA approved and is becoming commercially available. Results are reported as a number along a range of 0 - 200 with associated indications of the risk of diagnosing prostate cancer on biopsy. The scale by itself provides a prediction of a diagnosis of cancer on an initial biopsy, but also projects the risk of PSA failure after primary treatment. A nomogram (see below) incorporating easily available clinical data further improves these predictions.

Validated comparisons have shown that the PHI allows better discrimination between benign and cancerous prostate tissue and has improved specificity for predicting clinically significant cancer. The PHI is being further evaluated for its predictive accuracy in the selection of men for active surveillance and improving the prediction of the likelihood of recurrence.

Future impact of the PHI on screening policies:

It's hard to imagine that the PHI will not significantly impact the screening debate and it is likely to contribute to management decisions. However, it will take time for this new test to be incorporated into clinical practice.

A succinct review article was presented by Stacy Loeb and William Catalona, "The Prostate Health Index: a new test for the detection of prostate cancer," *Therapeutic Advances in Urology,* Vol.6, 2014.

As an example

> The mean PHI scores were 34 and 49 for men with negative and positive biopsies, respectively. Setting the sensitivity at 80-95%, PHI has a greater specificity for distinguishing the risk of prostate cancer on biopsy compared with PSA [a 47% improvement] or % free PSA [a 35% improvement].
>
> At the 2013 AUA meeting Dr. Sandra (Chairman of the Emory Urology Department) titled his report: "A more precise blood test outperforms traditional PSA screen test in detecting aggressive types of prostate cancer". Of 658 men with PSA levels between 4 and 10, 25% had PHI values <27% and only one man had a Gleason score of ≥4+3=7. Sanda suggested that this group of men might avoid biopsies.

In a 2014 *EMORY news center* publication Sanda presented additional data about the efficiency of the PHI test:

1) "At a 90% sensitivity, the specificity of phi was 31.1%, compared to 19.8% for %fPSA, and 10.8% for PSA;
2) A PHI score of 27 predicted the risk diagnosing cancer on biopsy at 9.8% and predicted a 3.9% risk of clinically significant cancer. A score of 55 predicted cancer at 51.0% and significant cancer at 28.9%;

PSA Test continued:

The FDA has approved the test for men with PSA values between 4 and 10. However, Catalona (*J Urol.2011 May)* reported that the PHI test functions well in the PSA range of 2 - 10 ng.ml.

The PHI also improved prediction of high-grade and clinically significant prostate cancer. The predictive accuracy was 70% for PHI, 65% for %fPSA, and for PSA, 55%.

Catalona contends: "These combined findings suggest that the use of PHI could significantly reduce unnecessary biopsies and the overdetection of nonlethal disease"

A PHI-based nomogram adds accuracy above that of the PHI alone: "Multicenter European Extramural Validation of a Prostate Health Index-Based Nomogram for Predicting Prostate Cancer at Extended Biopsy," (Lughezzani *et al.* European Urology. 2013). "The predictive accuracy [for diagnosing prostate cancer on biopsy] of the previously developed nomogram was 75.2%" and functioned particularly well "in patients with a low to intermediate predicted probability of PCa … ." The elements required for calculations with the nomogram were: patient age, DRE status, rebiopsy — yes or no, prostate volume, and PHI results over the scale of 0 - 200.

BOTTOM LINE: A schema of PSA testing based on risk-stratification combining a man's age and baseline PSA can reduce the number of biopsies required for efficient prostate cancer screening and guide in the selection of the best intervals between testing. When available, the PHI test, compared to the PSA, has the potential to better predict the appropriate candidates for prostate biopsy.

SEQUENCING THE NEW AGENTS IN THE TREATMENT OF METASTATIC CASTRATE-RESISTANT PROSTATE CANCER: Clinicians now have an abundance of riches but await guidelines for their best use.

For treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) clinicians now have six options, each having demonstrated improved prostate cancer-specific survival in randomized phase III trials:

Docetaxel	radium-223
siipuleucent-T ("Provenge")	enzalutamide (ENZA)
abiraterone (AA)	cabazitaxel

Drs. Sartor, Professor of Cancer Research, Tulane University, and Silke Gillessen, Professor of Hematology/Oncolgy, St. Gallens, Switzerland, in an analytically dense review have addressed this dilemma credibly —considering the lack of comparative data in "Treatment sequencing in metastatic castrate-resistant prostate cancer," *Asian Journal of Andrology,* March 2014. "None of the new agents have been compared to one another, thus physicians in practice today must make choices based on non-randomized comparisons, toxicity considerations and various assumptions."

These authors offer a succinct overview of the impact on median survival for the various available agents based on pivotal trials.

NEW AGENTS continued:

Median Overall Survival (OS) benefit (months) in metastatic castrate-resistant prostate cancer:

Docetaxel/prednisone vs mitoxanthrone/prednisone - 18.9 vs 16.5
(Became standard of care in 2004)

Used pre-chemotherapy: (In these trials patients were asymptomatic or minimally symptomatic.)

Sipuleucent-T vs control - - - - - - - - - - - 25.8 vs 21.7

Abiraterone/prednisone vs. placebo/prednisone - - OS not reached vs. 27.2
Endpoint of OS has not yet been reached (trial stopped early), but AA significantly prolonged time to radiographic progression vs control.

Enzalutamid vs placebo (PREVAIL TRIAL) - - - - 32.4 vs 30.4 (Truncated data)
(Trial was stopped early when ENZA at interim analysis showed significant benefit for prolonging radiographic progression and overall survival (30% reduction in the risk of death). Median time to chemotherapy was 28 months vs 10.8 for placebo. ENZA awaiting FDA approval in this context.)

Used post docetaxel chemotherapy:

Cabazitaxel/prednisone vs mitoxanthrone/prednisone - 15.1 vs 12.7
Abiraterone/prednisone vs placebo/prednisone - - - 14.8 vs 10.9
Enzalutamide vs placebo - - - - - - - - - - - 18.4 vs 13.6

NEW AGENTS continued:

Used before and after docetaxel chemotherapy:

Radium-223 vs best standard care - overall - - - 14.9 vs 11.3
pre-chemotherapy - - - - - - - - - - - - - 16.1 vs 11.5
post-chemotherapy - - - - - - - - - - - - 14.1 vs 11.3

"No agent has yet improved survival when co-administered with docetaxel/prednisone despite multiple attempts" (ibid, Sartor).

What are the take-away generalizations from the Sartor review?

In many practices abiraterone is now front-line for mCRPC making sequencing after abiraterone an important issue. "It is now clear that cross resistance is a potential issue between various treatments, especially those agents that target the androgen axis" [i.e. AA and ENZA]. To some degree, however, a lower response rate for an agent following a prior therapy may only reflect a higher burden of disease. There is no substitute for a randomized trial, which would be especially informative comparing AA with ENZA in early mCRPC pre-chemotherapy.

Cross resistance between AA and subsequent docetaxel has been suggested. The PSA response rate for docetaxel following AA, as measured by 50% PSA decline, was 26% versus 45%-57% for docetaxel with no preceding AA. The data is unclear if AA induces resistance to subsequent cabazitaxel. Cross resistance is not unexpected since all four agents interfere with the requisite translation of the androgen receptor (AR) into the nucleus. None of the agents address the aberrant AR signaling pathways that confer resistance to hormonal therapies.

Currently in clinical practice ENZA might likely be used subsequent to docetaxel and AA . Studies show a diminished benefit of third-line ENZA (measured as a >50% decline in PSA) — 29% as third line vs 54% in the AFFIRM trial when no intervening AA was used. Dr. Sartor concludes, "Thus although the data are minimal, there is clear evidence of cross-resistance between AA and ENZA … but some patients can still respond as measured by PSA declines."

Conversely, "Studies of abiraterone in patients previously treated with both docetaxel and enzalutamide … report a dramatic decrease in the activity of abiraterone compared to the expected." In two studies of AA following these two agents the PSA >50% decline response rates for AA are far less than expected: 13% and 8% respectively verses 29% and 51% as expected on the basis of phase II-III studies with abiraterone after only docetaxel.

Drs. Sartor and Gillessen freely acknowledge the limitation of their study but feel comfortable generalizing that "Data to date however suggest that whichever of these agents is used first will markedly diminish the activity of the second." They note the likely explanation is that "both target the ligand in the androgen-axis."

So what is a clinician to do? In the absence of guidelines, how about consensus among experts?

In the absence of evidence-based guidance, a European Consensus Panel was held in France in 2013. The results were reported the *European Journal of Cancer,* 2014, by Fitzpatrick *et al:* "Optimal management of metastatic castration-resistant prostate cancer." A multidisciplinary panel of 21 European experts in mCRPC fielded a total of 110 clinically-relevant questions.

The focus of this **Commentary** article will be on opinions relating to the issue of treatment sequencing in mCRPC. It is obvious from the responses that on many important issues there is difference of opinion. An assignment of "consensus" was made if agreement was ≥70% and "strong consensus" for ≥ 80%. The responses are instructive and thought-provoking:

1) Does prostate cancer exhibit histological/genomic heterogeneity within the same patient? **Yes; 100%.**

2) What is the best indicator of risk for primary resistance to AR pathway-targeted agents? Short duration of response to first-line androgen deprivation; **Yes, 86%.** … Rapid PSA doubling time? **No, 80%.**

NEW AGENTS continued:

3) When might radium-223 be used as monotherapy for mCRPC with symptomatic bone metastases? Predocetaxel - **Yes, 75%;** and postdocetaxel - **Yes, 80%**.

4) Is there cross-resistance between approved AR-targeted agents? **Yes, 90%**.

5) For a patient with disease progression on abiraterone, when should enzalutamide be considered?
   a) Consider using only if any clinical and/or biochemical response to abiraterone has occurred - **No, 67%**.
   b) Consider using only if a 'durable' response to abiraterone had occurred - **No, 76%**.
   c) Should be considered despite cross-resistance - **Yes, 85%**.

6) After disease progression on enzalutamide when could abiraterone be considered?
   a) Consider using only If any clinical and/or biochemical response to enzalutamide has occurred - No 76%.
   b) Consider using only if a 'durable' response to enzalutramide has occurred - **No, 76%**.
   c) Should be considered despite cross-resistance - **Yes, 86%**.

7) Is sipuleucel-T a reasonable option for asymptomatic or minimal symptomatic mCRPC? **Yes, 71%**.
   How should sipuleucel-T be positioned relative to other approved therapies?
   a) Before docetaxel - **Yes, 81%**
   b) Before abiraterone and/or enzalutamide - **Yes, 70%**.

8) When starting an AR pathway-targeted agent, which one would you use first:
   a) Abiraterone - **No, 85%**.
   b) Enzalutamide - **No, 65%**.
   c) It doesn't matter - **Yes, 71%**.

9) Should ongoing LHRH agonist or antagonist therapy be continued when a patient is starting on abiraterone or enzalutamide? **Yes, 95%**.

10) For a patient with a partial response to docetaxel and disease progression <6 month following docetaxel discontinuation, the next therapy should be …
    AR targeted agent, **Yes 95%**; Cabazitaxel, **Yes, 100%**.

    For progression after discontinuing docetaxel >6 months …
    AR targets agent, **Yes 100%**; Cabazitaxel, **Yes 100%**.

So that's a summary of expert opinion; … season to taste.

Late Entry: Abstract LBA2 presented at ASCO June 2014: Encouraging trial results for the relatively small group of men [hopefully declining in number with appropriate PSA testing] who presented at first diagnosis with metastatic disease: "Impact on overall survival with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer," Sweeney *et.al.* reporting an ECOG-led phase III randomized trial.

NEW AGENTS continued:

The study reported on 720 men, median follow-up of 29 months, who presented at diagnosis with hormone-naive metastatic prostate cancer. Half received standard androgen deprivation therapy (ADT); half received 6 three-week cycles of docetaxel in addition to ADT (within 4 months of starting ADT). The analysis was stratified according to the burden of disease with "high volume" defined as visceral metastases and/or ≥4 bone metastases, one being beyond the pelvis or axial skeleton.

The findings: Significant improvement in median estimated survival was seen in the high-volume cohort receiving the combination treatment: 49.2 months vs 32.2 months, a 40% reduction in risk of death. At 29 months there was a non-significant trend for benefit in the low-volume group but further follow-up is required.

This benefit in the high-volume group occurred despite subsequent chemotherapy in 40% of men initially having had only ADT compared to subsequent chemotherapy in 23 % of those having received combined therapy. Based on data combining both low and high volume disease, the median time to castration resistance was 20.7 months for combined therapy vs 14.7 months for the ADT alone arm; and for time to clinical progression was 32.7 vs 19.8 months.

Docetaxel was well tolerated; 74% of men received full therapy without dose modification or delays. However, not all men presenting with metastatic cancer will be candidates for chemotherapy, but those who are can benefit from this strategy.

BOTTOM LINE: This Commentary report summarizes the landscape of results for currently available agents for the treatment of metastatic castrate-resistant prostate cancer. The benefits from these agents are notable; but for many patients, disappointingly brief in duration. Additionally and unfortunately benefit is not experienced by all men. Regarding survival statistics expressed by "median," it is elating to be on the far end of the survival curve, but very disturbing to fall short.

The next chapter in treatment regimens will likely feature drug combinations, likely employing regimens based on rapidly improving immunotherapies.

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