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Contents

		Page
DIAGNOSTICS	Toward A More Specific Test For Diagnosing Prostate Cancer And Predicting Aggressiveness	**1**
QUALITY OF LIFE	"Prediction of Erectile Function Following Primary Treatment for Prostate Cancer." *JAMA* September 21, 2011	**3**

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DIAGNOSTICS: Toward A More Specific Test For Diagnosing Prostate Cancer And Predicting Aggressiveness.

The PSA test lacks specificity; only 25% to 35% of screened men with PSA values between 4-10 ng/ml are diagnosed with cancer on biopsy. An additional drawback, which fuels the current mantra "overdiagnosis/overtreatment," is the test's inability to indicate a cancer's aggressiveness.

Every prostate biopsy is attended by risk, albeit low, of bleeding, infection, and, very infrequently, hospitalization. The goal of improved test specificity is to entirely avoid, or at least minimize, unproductive biopsies.

What technological advancements lie ahead to rectify this deficiency? The current trend is toward the use of molecular biomarkers in blood and urine to a), more specifically diagnose cancer; and b), to better identify patients who are at higher risk for fatal prostate cancer.

1) Assessment of the PCA3 Urine Test for Initial Diagnosis of Prostate Cancer.

The search for the proper role for the PCA3 test is robust, especially in Europe. Two points are already clear: 1), PCA3 gene products are highly overexpressed in prostate cancer tissue and can be accurately identified in the urine; and 2), the "PCA3 is superior to the PSA and the percent free PSA in the early detection of PCa" *(Auprich Eur Urol Nov 2011)*.

As a stand-alone test for initial diagnosis the value of the PCA3 test is limited. Men with test values of >35 are considered candidates for biopsy, but the real usefulness of the test may accrue from its strong negative predictive value for low values. "A PCA3 score threshold of 20 may have the highest utility for selecting men with clinically insignificant disease in whom active surveillance may be appropriate." (*van Poppel, BJU Int 2011 Aug*).

However, the ***addition*** of the PCA3 test to standard tools improves their predictive accuracy. The commonly used nomogram, "Prostate Cancer Prevention Trial Risk Calculator"(http://deb.uthscsa.edu/***URORiskCalc/Pages/calcs.jsp*** estimates the likelihood of finding cancer on biopsy. Its accuracy is increased by the addition of PCA3 vales. Take for example a 69 year old Caucasian man, PSA 4.6 ng/ml, DRE negative with no family history of cancer. The calculator prediction of a positive biopsy is 32.8% if his PCA3 test is 20, and rises of 46.1% if the value is 57, and risk increases as the PSA3 values rise.

2) The forthcoming PCA3/TMPRSS2:ERG Urine Test.

A new hybrid urine test has been developed at the University of Michigan. It improves specificity by combining two biomarkers: the *TMPRSS2:ERG* gene fusion product, present in 50% of prostate cancer patients, and the PCA3 (prostate cancer antigen 3) expressed at high levels in 95% of prostate cancer patients. This test was co-developed by Arul Chinnaiyan, MD, PhD, and Scott Tomlins, PhD, who explained the need for a hybrid test: "There is no one biomarker for every prostate cancer."

The *TMPRSS2:ERG* "fusion" gene is associated with accelerated prostate cancer growth. The "new" gene combines (hence, termed a "fusion") a portion of an important gene product in the signaling chain that activates the androgen receptor with a fragment of another gene that "turns on" the expression of the new construct, the *TMPRSS2:ERG* gene.

Recent results from early testing were described by Tomlins in *Science Translational Medicine 2011 Mar: "Urine TMPRSS:ERG* Fusion Transcript Stratifies Prostate Cancer Risk in Men with Elevated Serum PSA." The test is scored from 0-100 based on the combined level of detection of the two gene products, TMPRSS2:ERG and PCA3. Results are stratified in categories of low, intermediate and high levels.

Results: Men testing in the low category have only a 20% chance of being diagnosed with prostate cancer, and 7% likelihood of harboring high-risk disease. Men with high levels run a 70% chance of a cancer diagnosis and a 40% chance of high-grade disease.

Inclusion of values of this test further improves the performance of the Prostate Cancer Prevention Trial risk calculator.

A national study of this test is underway conducted by the NCI in cooperation with the Early Detection Research Network (EDRN). Until the availability of the test is more widespread the test will be offered by the University of Michigan. For information call 800-865-1125.

3) Five-Gene Prognostic Marker for Prostate Cancer-Specific Mortality [PCSM].

In addition to our needing a more specific biomarker to improve or supplant the PSA, there is also a great need for a tool to predict cancer's aggressiveness once a diagnosis of cancer has been made. The standard categories of risk that build upon the PSA, Gleason score, and tumor stage are generally useful, but hidden within each grouping there are particular cancers that bode a far worse outcome than a clinician might predict based on the usual metrics.

A glimpse into the future for the search for such a indicator of cancer aggressiveness is presented in an article by Janet Stanford, PhD, Dan Lin, MD, of the Fred Hutchinson Cancer

Research Center along with international colleagues. It appeared in *Cancer Epidemiol Biomarkers Prev, September 2011.* Their research produced a five gene signature, the "first population-based study to show that germline [inherited] variants provide information for prostate cancer-specific survival." These germline variants are analyzed in blood samples.

They found a compounding effect on risk based on the five abnormalities. "Compared with patients with 0-2 of the at-risk genotypes those with 4 to 5 at-risk genotypes have a 50% ... higher risk of PCSM." Higher risk was associated with "an increasing number of at-risk genotypes carried, *adjusting for clinicopathological factors known to influence prognosis"* [italics mine].

The "at-risk" factors identified in the study are single nucleotide polymorphism, "SNPs" - read "snips." A SNP is an individual alteration from the normal of one coding element, i.e. one base pair, in the many thousands that string together to make a gene. These minute differences in the makeup of these 5 genes "were associated with significant differences in survival among prostate cancer patients."

The names of these genes are very likely unfamiliar to clinicians: *RNASEL,* the *leptin receptor, Interleukin 4, Cryptochrome 1* and *ARVCF.* Their various functions relate to angiogenesis; cell proliferation, adhesion, migration, and invasion; bone mass regulation; and regulation of the circadian rhythm controlling androgen levels. Taken together, SNPs in these genes drive cancer progression.

Stanford's study is but one example of the direction of research aiming at better estimating cancer aggressiveness. Dr. Stanford commented that a combination of germline and somatic (acquired) changes may provide better prediction. Their next effort will be "to incorporate germline, somatic, and clinical factors to evaluate associations with prostate cancer recurrence/progession and PCSM."

BOTTOM LINE: Important advances are under development that improve both the specificity of testing for prostate cancer and the accuracy of predicting disease of clinical significance.

QUALITY OF LIFE: "Prediction of Erectile Function Following Primary Treatment for Prostate Cancer." *JAMA* September 21, 2011

This article, authored by Dr. Martin Sanda and colleagues, compiled data from 9 US university-affiliated hospitals between 2003 to 2006 regarding erectile function. They had follow-up on 1027 men 2 years after primary therapy. Dr. Sanda is Associate Professor, Department of Urology, Harvard Medical School and Director of the Prostate Center. He researches and writes about quality of life issues relating to prostate cancer.

The study "focus[ed] on the end point of erections 'firm enough for intercourse' to provide a concrete metric having practical relevance to routine clinical care." In responding to this questionnaire men were asked to consider their erectile status during the prior 4 week period.

Public interest in the observations presented in this article is attested to by the numerous citations in major newspapers and journals across the nation including the Tuesday Science section of the New York Times. The authors' findings make a major contribution to appreciating the adverse consequences upon erectile function of *any* form of primary treatment - surgery, radiotherapy, or brachytherapy. Clinicians know that for many men preservation of sexual performance is a pivotal issue in their choice of primary therapy.

The unique contribution of the article lies in the nuancing of risk based on individual patient characteristics and treatment variables.

What was already known about this subject?: It has been generally recognized that all primary treatments - each to a varying extent, effect a deterioration in erectile function; that data should be collected prospectively and based on patient reporting; and that functional loss should be evaluated in comparison with the individual's baseline erectile performance.

Excellent earlier work on this issue has been presented by Talcott and Litwin in past publications: (Reviewed in past PCa Commentaries listed under "Quality of Life")

In Talcot (JCO Nov. 2003) *loss of function* at 24 months from baseline after non-nerve sparing surgery was about 35%; for external beam radiotherapy, 20%; and for brachytherapy 16%. Increasing age led to worse dysfunction.

In Litwin (JNCI June 2009) the observation period was extended to 48 months and presented in graphic form which roughly showed a loss from baseline for surgery of ~20%, for external beam radiotherapy and brachytherapy slightly less. Their summary: "Sexual dysfunction was profoundly affected by all three treatments, with the lowest likelihood of regaining baseline function after prostatectomy

CAVEAT REGARDING THESE FIGURES: It is wholly misleading to think that these figures apply to each and every man. These figures were not stratified for many important individual variables, and it would be a mistake for a clinician to counsel a man about his risk with overall figures such as these. A man's particular outcome could vary widely above or below these estimates *according to his individual characteristics*. The added value of the recent JAMA study is taking into account these individual features.

SUMMARY OF FINDINGS IN THE JAMA ARTICLE - the "Cliff Notes":

Who was studied and why focus on 2 year follow-up?

All men had T1 or T2 prostate cancer. Of the 1027 men forming the basis for the predictions generated in this study, 524 had a prostatectomy, 241 were treated with external beam radiotherapy, and 262 underwent brachytherapy. Importantly, the results were validated against 1655 men registered in the CaPSURE data base and found generally applicable.

The authors cite studies that suggest stabilization of changes in erectile function at 2 to 3 years following treatment, but allow that after 2 years there may be some improvement in erectile function for men after surgery, and some further deterioration of function after radiotherapy.

What individual pretreatment characteristics adversely affecting outcome were common to all three treatment modes?

These included: increasing age; increasing cancer severity (higher PSA and Gleason score); baseline erectile function (gradations from none/poor through intermediate to optimal function); race/ethnicity (white/other worse than African American); and an increasing number of comorbid conditions, such as diabetes and cardiovascular disease.

What pretreatment features were unique to each treatment type?

Regarding radical prostatectomy: Since this was a prospective study, "intent to perform nerve sparing" was the metric used in the analysis of prostatectomy outcome. This choice has obvious limitations compared to an evaluation based on the actual surgical procedure performed. Nonetheless, those men in whom there was an "intention" to spare nerves fared better than those in whom there was not an expectation of success.

Regarding radiation therapy: Men receiving adjuvant hormone suppression had a greater deterioration in subsequent function compared to non-users. For brachytherapy a higher body mass index was associated with worse erectile function, possibly due to technical factors relating to seed placement.

General outcome results:

For men who were *potent prior to treatment*, what were the "*gross overall*" figures after 2 years of follow-up indicting the percentage of men who *lost erectile function*?: In the prostatectomy group 60% lost erectile function; for external beam radiotherapy, 42%; and for brachytherapy 37%.

But again these findings carry the same CAVEAT for as the general outcome figures in Talcott and Litwin, e.g. individual characteristics must be considered since predicted probabilities vary "from as low as 10% or less to as high as 70% or greater depending on the individual's pretreatment characteristics and treatment details."

Useful Tables for the Office:

Key probability findings were presented in three tables. The question relating to quality of erections on the EPIC-26 Quality of Life Questionnaire was grouped as: 1) none at all; 2) not firm enough for any sexual activity; 3) firm enough for masturbation and foreplay only; and 4) firm enough for intercourse. Each table presented "Predictive Probabilities of Men Having Function Erections Suitable for Intercourse 2 Years After [a treatment type]." The probabilities were listed in three columns based on the actual results of the study group's experience: column #1 - significant erectile dysfunction [ED] (36% respondents listed this); column #2 mild ED (45% reported this); and no ED (19% of respondents).

An example from Table 2 for prostatectomy patients: A 60 year old man, PSA <10 ng/ml, in whom nerve sparing had been planned, whose pre-surgery erectile dysfunction was mild was estimated to have a 38% (range 33-44) chance of functional erections 2 years after surgery.

An associated set of three additional graphs for prostatectomy patients relate PSA and intent for nerve sparing with separate graphs for men age 50, 60, and 70. As expected, function worsened with increasing age.

An example from Table 3 for external beam radiotherapy patients: A man, PSA level ≥4 ng/ml, having had EBRT and no neoadjuvant hormone therapy whose pre-treatment erectile function was 100% would be predicted to have a 79% (range 67-87) chance in two years for functional erections. With hormone therapy the prediction dropped to 53% (range 35-71).

An example from Table 4 for brachytherapy patients: A 70 year old white man, BMI 25 - <35, whose pre-treatment dysfunction was mild would be predicted 2 years later to have a 47% (range 34-60) chance for functional erections. For an African American man with the same characteristics the prediction is 73% (range 45-90).

The take-home message clearly is that in order for a clinician to counsel a patient regarding predicted erectile performance he would need to estimate a final prediction by merging together these many relevant factors.

BOTTOM LINE: Sanda and colleagues convincing establish that there is no simple answer - no single number, to the question about which mode of primary treatment best preserves erectile function. Their valuable contribution to this important consideration is that many factors individually and collectively affect a man's outcome.

But keep in mind Yogi's advice - "Prediction is hard especially about the future."