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"Prostate Cancer, Genetics, and Giving More Accurate Medical Advice"

The Human Genome Project, an incredible scientific feat, characterized the sequences of genes that make us who we are, and has led to discovery of which proteins are coded by which gene sequences. Contrary to prior teachings, the majority of gene sequences does not code for specific proteins, but may be involved more in the regulation of these gene products. This has medical relevance in that changes in or so-called under or over-expression of these proteins can be used as "markers" for certain cancers; and knowledge of the differences between proteins produced by cancerous versus normal cells has and can lead to targeted therapies potentially replacing the current less specific treatments for e.g., advanced prostate cancer. Now that thousands of human genomes have been sequenced, the differences in genomes among humans @ 0.1% is only 10% of the difference between any human and the closest primate relative (chimpanzee).

Genetic testing is increasingly making its way into prostate cancer diagnosis. Although the validity of such tests is known, the exact role in decision-making for the clinician is less obvious. The results will not always change a cancer patient's decision. There are also high cost issues; and as is typical for any medical testing, false negatives (normal result when there really is something wrong) and false positives (abnormal result when "all is fine").

I wanted to share with you a few of the "newer" tests; what they measure; and in what clinical decisions regarding prostate cancer they may be of assistance.

We know that prostate biopsies have at least a 10%, and perhaps (in some studies), 20% chance of being falsely negative. That is, a man has prostate cancer but the biopsy does not detect it. Random biopsies, often 12 in number, sample a small percentage of prostate tissue, and can miss a small amount of cancer, more so if there is no lump felt by the urologist and no specific sonographic abnormality

at the time of ultrasound-directed biopsy. So the questions are: “can we trust the negative biopsy results?” and "what can be done after a normal biopsy other than close clinical follow-up and perhaps re-biopsy at a later date?” The MATLOC (methylation analysis to locate occult cancer) study, completed last year, demonstrated the utility of looking for excessive (“hyper-“) methylation of certain nucleotides (building blocks of DNA) to predict, from a genetic/biochemical point of view, the probability of actual cancer in a prostate specimen read as negative by the pathologist. To keep it simpler, let us say that methylation is a reaction to add a so-called “methyl” group to a DNA component. Normal methylation is an everyday process and tends to stabilize cell division and differentiation of primitive to more specialized cells. Hypermethylation (and deficient, or hypomethylation) are associated with certain cancer states. When such tests on prostate tissues (even on “old” preserved biopsy specimens) are performed using a commercially available test (Confirm MDx), hypermethylation--as tested on three separate genetic foci--can not only detect which biopsy cores show methylation, but can predict that these hypermethylated cores, with 80% accuracy, are correlated with the next (2nd) biopsy of the same areas showing prostate cancer. Note that about 95% of positive prostate biopsies will demonstrate the high methylation reaction.

In this era of doubts about the benefit of PSA screening and even about whether low grade (less aggressive-appearing) prostate cancers require treatment, how do we advise men on whether to be placed in an ”observation” or “treatment” category? There are men now in their 50’s, with newly diagnosed prostate cancer, choosing active surveillance, a form of observation that includes no treatment but close clinical follow-up and repeat biopsies. Are all low-grade prostate cancers alike? Is it safe for a man with a Gleason pattern 6 or 7/10 prostate cancer (as determined by the pathological review of the biopsy) to avoid curative treatments, on a bet the cancer will not progress and given the desire to avoid side effects of aggressive prostate cancer treatment? Something called the CCP or cell cycle progression score can be derived by looking at the expression of proteins from 31 genes felt to be important in the proliferation and aggressiveness of prostate cancer cell behavior. These 31 genes are compared to

15 other “housekeeper” genes in the man’s DNA that are not involved in promoting cancer--so as to “normalize” the amount of genetic protein expression from one subject to another. For simplicity, let us say that the CCP score--by itself--seems to predict better than the PSA or Gleason score alone (or the two in combination) the rate of growth/spread of the tumor and indeed, the chance of death from untreated prostate cancer in a 10-year time frame. The commercially available Prolaris Test (Myriad Labs) combines this CCP genetic information with a CAPRA (Cancer of the Prostate Risk Assessment) score, based on non-genetic parameters, to increase the power to differentiate low risk cancers with low potential to do harm--from low risk cancers with higher potential to progress and cause problems. For example, a Prolaris Score of 1.8 for one man with a pre-biopsy single digit PSA, low percentage of biopsy cores involved and no palpable tumor on digital exam may predict a 5% risk of prostate cancer death over 10 years; a similar man with the same clinical pattern and a low Prolaris score of -1.1 will have a 1% ten year mortality risk. One “problem” to be considered in this test is that in general, with Gleason 6/10 prostate cancers, very few men will die of the disease--even if left untreated-- within 10 years of the time of diagnosis of localized disease. However, a man in his 50’s or 60’s, contemplating observation and seeing that his Prolaris score predicts a low, albeit 5x (5% versus 1%) chance of dying of cancer in the first ten years after diagnosis, may conclude that he could indeed eventually die of untreated prostate cancer—therefore may decide on radical surgery or radiotherapy to try to eliminate the cancer.

Just as immunologic staining of cancer tissues for proteins has pushed cancer pathology into a new era of precision and made pathologic diagnoses more certain, so do newer genetic tests (the ones above only being examples) help us as urologists to answer specific questions about an individual's risk from prostate cancer and to give better advise.

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