

Testing/Diagnostics

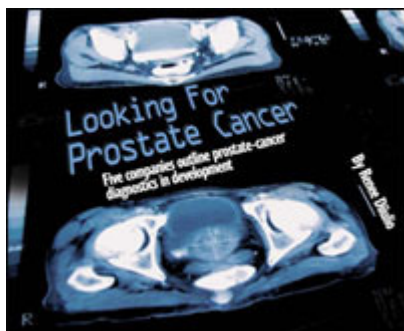
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Looking for Prostate Cancer

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by Renee DiIulio

Five companies outline prostate-cancer diagnostics in development



Prostate cancer is the most common cancer among men and the second leading cause of cancer-related death. The American Cancer Society estimates that prostate cancer will be diagnosed in one in six men, and one in 35 will die as a result. More than 2 million men in the United States are living with a prostate-cancer diagnosis, and more than 218,000 men have had the disease diagnosed in 2007.¹

The good news is that most prostate cancers are found before they have spread to distant sites, and the 5-year survival rate for these men is nearly 100%. The 5-year survival rate for men in whom the cancer has spread is roughly 32%.¹

Earlier diagnosis can be credited with some of the positive news regarding prostate cancer. The prostate-specific antigen (PSA) test, according to R. Jeffrey Karnes, MD, department of urology, Mayo Clinic, Rochester, Minn, "has dramatically increased the incidence of prostate-cancer diagnoses over the past 25 years, and we are diagnosing men at a younger age and a younger stage. The real challenge is not in making the diagnosis but in deciding who needs treatment."

PSA, which is the current gold standard for prostate-cancer screening, has a high false-positive rate: by some estimates, approximately 75% of men referred for prostate biopsies have a negative result. Karnes suggests that knowing the PSA value over time could provide better information. "A PSA value that is going up, but still within normal values, may be a sign of prostate cancer," Karnes says. Newer diagnostics, however, may be able to provide better information with one test value. Karnes notes that there are thousands of research projects seeking to identify better biomarkers to improve the specificity of PSA testing (or even replace it).

DNA Methylation

Epigenomics Inc, Seattle, has a number of such tools in development, both diagnostic and prognostic. Achim Plum, PhD, Epigenomics' vice president, corporate communications, says, "We have two types of tests: early-detection screening diagnostics that work on a body-fluid sample and molecular-classification tests that provide prognostic value."

The company is exploring DNA methylation biomarkers as a means of recognizing free-floating tumor DNA. "We know that tumor cells have a very specific DNA methylation fingerprint," Plum says. By identifying the pattern of methyl groups on the DNA, the test can reveal not only the presence of a tumor, but also its origin.

Epigenomics has identified a number of biomarkers related to prostate cancer. "The problem we often see in markers is the same as that with PSA: It's hard to distinguish between prostate cancer and conditions such as benign prostatic hyperplasia," Plum says.

To increase a new test's ability to distinguish between malignant and benign conditions, the company has focused on discovering markers that are associated with prostate cancer only. "We have found a number of good marker candidates on tissue and selected 38 for more specific assay development and testing," Plum says, adding that they will eventually be developed for urine testing. The company hopes to have a validated biomarker panel, which would then be commercialized, toward the end of 2008.

Epigenomics also plans to bring its prostate-cancer prognostic test to the US market in 2008. "We can look at the DNA methylation fingerprint in tumor tissue and answer questions about aggressiveness and potential recurrence," Plum says. The information may help the physician to make more informed treatment decisions. The test will run on the IVD system by Affymetrix, Santa Clara, Calif, a company with which Epigenomics has a development partnership.

Gene Fusion

Gen-Probe Inc, San Diego, has developed a test that also may be available soon in the United States: the prostate-cancer antigen 3 (PCA3) assay. The in vitro nucleic-acid-amplification test generates a PCA3 score using quantitative measures of PCA3 mRNA in urine specimens in calculations involving PSA. Hank Nordhoff, Gen-Probe's chairman, president, and CEO, says, "PCA3 is expressed in both healthy and cancerous prostate tissue, but is overexpressed 60-fold to as much as 100-fold by cancerous tissue."

Nordhoff notes that the positive predictive value of PCA3 is about 75%, calling that "the flip of PSA." The test is already available in Europe, where it is CE-marked, and is available in the United States as an analyte-specific reagent. "The test is not intended to replace PSA. but it does provide additional information to help the physician make better treatment decisions," Nordhoff says.

Further away from commercialization is Gen-Probe's work with gene fusion and TMRSS2, a prostate-cancer fusion gene licensed from the University of Michigan, Ann Arbor. "TMRSS2 is the first gene fusion found in solid tumors, and we think it may be the cause for about 65% of prostate cancers," Nordhoff says.

Prostate Cancer Diagnostic Marker 1

Specificity is just one problem with current diagnostic methods, according to Mark Stearns, PhD, president and chief scientific officer of MacroArray Technologies LLC, Villanova, Pa. The other two problems are the 35% incidence of latent cancers in which the patient has the prostate removed unnecessarily and the need to identify premalignant prostate cancer, known as prostatic intraepithelial neoplasia (PIN).

MacroArray has developed a standard, urine-based enzyme-linked immunosorbent assay (ELISA) using the prostate cancer diagnostic marker 1, which has shown a sensitivity approaching 85% and a specificity of about 80%. The test has been licensed to Abbott Diagnostics, Abbott Park, Ill, which will adapt it to the Architect system and obtain FDA approval. Nordhoff estimates that the process will take about 2 1/2 years.

The test has been designed to reduce PSA false positives and pathology false negatives. "The test will eliminate those who do not need to be biopsied, as well as pick up the 15% of patients whose biopsies are missed for cancer," Stearns says.

MacroArray expects the test to replace the PSA test, but it is developing tools meant to complement prostate-cancer screening tests. One such marker is that for high-grade PIN. "PIN-diagnosed patients go on to develop cancer at a rate of about 50% within 3 to 5 years of the PIN diagnosis," Stearns says. Early and appropriate treatment can help prevent the condition from progressing to cancer; MacroArray is collaborating with GTx Inc, Memphis, Tenn, which has developed a PIN treatment. The company also hopes to develop a urine test for physicians' offices and a take-home test for patients. "Patient compliance with prostate screening in men over 50 is 19%," Stearns says. Easy, rapid, urine-based tests may help improve that figure.

Protein Biomarkers

Miraculins Inc, Winnipeg, Manitoba, is also developing a test intended to improve the specificity of PSA. The P2V test, however, is intended for use in conjunction with existing PSA tests, not as a replacement. Christopher J. Moreau, president and CEO, says, "The test has two utilities. It can help reduce the number of men who undergo a biopsy, and it has a higher capability to differentiate high-risk and low-risk cancers."

The test's use would further narrow the population sent for biopsies by one fourth. "Our test would eliminate one of every four negative biopsies, and we anticipate improving that number as we refine the test," Moreau says.

Biopsies are not only unpleasant, but also carry risks to the patient and are expensive. "The entire urology costs of a biopsy run about \$2,500, so 750,000 patients will have about \$3 billion in biopsy costs. Unnecessary procedures account for \$1.5 billion," Moreau says, noting that the \$3 billion figure includes many men who undergo more than one biopsy.

The technology is based on proteomics. "We have found two proteins that behave differently in cancer-group populations when compared with noncancer groups," Moreau says. The company is currently working with the FDA to determine the parameters of its final study in the commercialization of a corresponding ELISA. According to Miraculins, the test's protein biomarkers are able to distinguish aggressive prostate cancer (defined as cancer with a Gleason grade of 7 or higher) from nonaggressive prostate cancer with a sensitivity and specificity of 92% and 55%, respectively.²

Human Aspartyl (asparaginy) [Gk Ic b]-Hydroxylase Biomarker

PC Detect by Panacea Pharmaceuticals, Gaithersburg, Md, also improves the sensitivity and specificity of a PSA test and is meant to be used in conjunction with the existing screening method. The test works by measuring levels of the biomarker human aspartyl (asparaginy) [Gk Ic b]-hydroxylase (HAAH). "We've demonstrated this to be a sensitive and specific marker for cancer, and it significantly improves the ability to predict which men will actually have cancer and which have elevated PSA for other reasons," Stephen N. Keith, MD, MSPH, Panacea president and COO, explains.

HAAH can help indicate more accurately which men should undergo biopsy. Though it is not specific to prostate cancer but to cancer in general, given the high incidence of prostate cancer, a male over age 50 has a high likelihood that an elevated HAAH level is related to prostate cancer.

The enzyme biomarker also can help in screening for the recurrence of prostate cancer. "Theoretically, after treatment, your HAAH should return to zero, while PSA may remain elevated, so this is a very sensitive way of looking for recurrence of disease," Keith says.

Keith notes that, in addition to having a sensitivity and specificity higher than those of PSA, HAAH is a simple, inexpensive blood test available through Panacea for \$125. The company is developing a kit that is expected to be available to clinical laboratories sometime in 2009.

"It can be frustrating for urologists to make a determination as to which patients need biopsies. They take several factors into account—patient history, physical exam findings, and PSAs—but they become excited about tools that can help to identify which men should have a biopsy," Keith says. When these products come to market, clinicians will have those tools.



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Renee DiIulio is a contributing writer for CLP.

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