



ADVANCES

From the CEO

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April 2009



Special Issue: *Reaching Beyond the PSA Debate*

The recent publication of two studies in *The New England Journal of Medicine* challenging the usefulness of PSA testing in men reinvigorated a long-standing debate and initiated a wave of media stories. These stories raised issues associated with PSA screening.

The stories generated anxiety about over-diagnosis with excessive biopsies, and in some cases, possible over-treatment of men who do not have lethal cancers at diagnosis. With over-diagnosis has come the renewed discussion in the media of the potential for unnecessary side effects in men who elect to undergo active treatment.

Unfortunately for patients, rather than providing clarity, this most recent round of public discussion may have done more to confuse than to help the very men it was intended to serve. What these news articles failed to emphasize is the need for research and development of new laboratory tests that can end the debate and deliver better treatment decisions for every patient. What is needed are **new** biotechnologies in the clinic that can distinguish between different prostate cancers—those that are aggressive and potentially lethal, versus those that are indolent and unlikely to ever cause harm in the life of the patient.

Within hours of the March 18 *New York Times* story reporting on the studies, the Prostate Cancer Foundation posted its perspective on PSA testing on the home page of our website, pcf.org. Here is the full text of that statement:

PCF Perspective on Recent *New England Journal of Medicine* Reports Concerning PSA Screening

Recent publications in the *The New England Journal of Medicine* question the effectiveness of PSA screening in reducing death from prostate cancer. These reports, from large randomized trials performed in North America and Europe, generated conflicting results. Analysis of the North American study showed no reduction in prostate cancer mortality attributable to PSA screening, while a 20% reduction in mortality was observed in the European study. Both investigations contained important information about PSA screening. As with any trial, there are complex methodological issues to be considered and the medical community will be evaluating these trials in more depth.

The PSA test, with its limitations, remains an important tool in the diagnosis and treatment of prostate cancer. At this point, specific clinical recommendations cannot be made and are best left defined within the patient-physician relationship.

The Prostate Cancer Foundation (PCF) actively funds global research aimed at creating new laboratory tests focused on improving the early diagnosis of prostate cancer. Unlike PSA, which is not cancer-specific, the methods we seek are those that would provide early identification of potentially lethal prostate cancer. These optimal tests will reduce unnecessary biopsies and resulting treatment morbidity. Stewarding research to develop such tests for clinical practice is a significant PCF goal.

Much progress has been made, yet more needs to be achieved. The PCF will continue to advocate for both private and government funding of prostate cancer research programs to advance more specific diagnosis, prognosis, and improved treatments for prostate cancer.

For the present, patients need to remain active participants in their health management in partnership with their physicians. Physicians need to fully present the pros and cons of PSA screening and, if necessary, treatment options.

A complementary web video presenting a scholarly discussion on these issues is available at <http://www.nejm.org/perspective-roundtable/screening-for-prostate-cancer/>. This video features commentary from Philip W. Kantoff, MD of the Dana-Farber Cancer Institute. Dr. Kantoff is a member of the [PCF Therapeutic Clinical Investigation Consortium](#).

The purpose of the PCF is to one day put ourselves out of business by ending death by prostate cancer. To reach that goal, we are committed to funding research that can replace the existing PSA test and deliver new, more specific diagnostic tools.

[NEJM Discussion Transcript \(PDF\)](#)

[Learn more about PCF-Funded Research](#)

[Read About the Latest Developments from PCF's 2008 Scientific Retreat \(PDF\)](#)

PCF also pushed the statement to our entire e-mail subscriber list of more than 37,000 individuals. Traffic to pcf.org was up by nearly 3,500 visits that day as a result of that communication.

Additional Coverage

The Prostate Cancer Foundation has been working proactively for some time with health and medical research media representatives, providing background on the Foundation and the research programs it supports. Given the tremendous response to *The New York Times* article, *The Wall Street Journal* decided to produce a two-part series on prostate cancer that began on March 30. We provided the first *WSJ* article with extensive background for the series. PCF's perspective and much of the research it supports is represented in the article. These two stories can be accessed through the following links:
<http://online.wsj.com/article/SB123845699393571631.html> and
<http://online.wsj.com/article/SB123906164489395123.html>

The Resounding Conclusion: More Research is Crucial

The ultimate answer is we need research that delivers to patients better tests than the measurement of PSA alone. PCF has been funding that “better biomarker” research long before the latest *New York Times* article. It is crucial that we at PCF help facilitate the discovery and development of new prostate-cancer-specific laboratory tests that will enable the medical community to identify the cancers that will not cause a problem in a patient's lifetime. We also need tests that identify the potentially lethal prostate cancers that need immediate treatment. In that way, the best treatment plan can be developed to treat each patient.

Even with its limitations, the PSA test remains an important tool in the diagnosis and treatment of men with prostate cancer, along with other diagnostic tools, plus the prostate examination. Dr. Peter Scardino states this in the *WSJ* article. In addition, patients need to be *active advocates* of their healthcare, armed with *balanced* information, so patients can engage in two-way discussions and planning with their physicians.

With your support, PCF-funded scientists around the globe are working to develop advanced solutions that should ultimately eliminate the confusion and “end the debate” surrounding PSA screening. The PCF is actively engaged in funding several promising programs in this area. Below are five unique, ingenious, and prostate-cancer-specific programs focused on biomarkers in urine and blood that could ultimately replace the PSA test. Below, I am reviewing again those research efforts and a summary and list of key findings from each of these programs.

1. PCA-3 and Gene Fusion Urine-Based Diagnostics of Prostate Cancer

Jack Schalken, PhD, Research Director of Urology
Nijmegen Center for Molecular Life Sciences (The Netherlands)
PCF Competitive Award Recipient

Arul Chinnaiyan, MD, PhD, Professor of Pathology and Urology
Michigan Center for Translational Pathology
University of Michigan

Jack Schalken, PhD from the University of Nijmegen in the Netherlands and Arul Chinnaiyan, MD, PhD from the University of Michigan are developing two important molecular diagnostic tests in urine for prostate cancer. One detects the presence of PCA-3 (Schalken), a prostate cancer-associated gene, and the other tests for the presence of the gene fusion TMPRSS2-ERG (T2-ERG; Chinnaiyan) responsible for up to 60% of prostate cancer cases. Both of these tests can be performed on cells found in urine. These markers are found only in cancer cell DNA, so, unlike PSA, both are specific markers for prostate cancer.

Currently, the PCA-3 test is approved for diagnostic use in Europe and is widely available at reference labs in the U.S. Schalken's and Chinnaiyan's findings suggest that these tests may be superior to PSA with respect to identifying patients that might need aggressive therapy. Research on T2-ERG detection in urine is at an earlier stage of development. The assays are not mutually exclusive. Dr. Schalken noted at our 2008 Scientific Retreat at Lake Tahoe that information on diagnosis and prognosis will likely increase by combining results from these molecular tests with other clinical and laboratory findings. These genetic tests are under development by Gen-Probe, Inc., led by its CEO and PCF Board member, Hank Nordhoff.

Key Findings:

- PCF funding in the 1990s resulted in the discovery of the gene DD-2 which has been renamed PCA-3.
- PCA-3 is the first DNA diagnostic test for prostate cancer to be discovered by comparing prostate tumor DNAs to normal DNAs.
- PCA-3 is being rigorously tested in multiple clinical settings in Europe and the U.S. for the diagnosis of prostate cancer.
- PCA-3 biomarker may have a significant impact on the diagnosis and staging of prostate cancer configured as a urine test.
- A second molecular test under development is the detection of a gene fusion thought to be the cause of up to 60% of prostate cancers (T2-ERG).
- Both PCA-3 and T2-ERG tests are receiving developmental support from the U.S.-based company, Gen-Probe, Inc.

2. Circulating Micro-RNAs as Stable Blood-Based Markers for Cancer

**Muneesh Tewari, MD, PhD, Assistant Member, Human Biology
The Fred Hutchinson Cancer Center (Seattle, WA)
*PCF-Arnie's Army 2009 Creativity Award Recipient***

Dr. Muneesh Tewari from The Fred Hutchinson Cancer Center at the University of Washington discovered miR-141 which is a cancer-associated micro-RNA. His focus is on the characterization of micro-RNA and the development of a micro-RNA-based diagnostic test to identify prostate cancers with a simple blood test. Tewari was studying a micro-RNA designated miR-141, and others, when he asked the simple question: Could this micro-RNA be detected in the blood of patients with prostate cancer? Tewari was aware that micro-RNAs showed unusually high stability in tissue specimens. On a hunch, he decided to test whether this stability extended to blood as well.

In Seattle, a PCF-funded group, headed by Drs. Peter Nelson and Robert Vessella, has been assisting Dr. Tewari as collaborators with prostate cancer expertise. Dr. Tewari, who was not a prostate cancer expert a year ago, is now collaborating daily with some of the world's leading scientists whose laboratories are in immediate proximity. An important principle for biomarkers is that although PSA is prostate specific, it is not cancer specific. Both normal and malignant prostate cells produce PSA, causing PSA levels to change for a host of reasons that are not necessarily related to cancer progression.

This micro-RNA may prove to be more prostate-cancer-specific and is not changed by hormone treatment. This may allow more precise assessment of prostate cancer growth or regression after a given treatment. Dr. Tewari has developed a test to measure miR-141 and other cancer-specific micro-RNAs in human blood samples. Tewari's work, being supported by the PCF Golf Program, Arnie's Army Battles Prostate Cancer (www.arniesarmybattles.com) might also be applicable to patients with other solid tumors, especially ovarian cancer.

Key Findings:

- Some micro-RNAs are made only by cancer cells, not normal cells.
- Exosomes are membrane particles released from cancer cells that contain debris.
- Small regulatory RNA molecules, termed micro-RNAs, are stable in blood and are found in exosomes.
- Laboratory models proved that prostate cancer-derived micro-RNAs can be detected in blood within exosomes.
- Levels of one micro-RNA, designated miR-141, identify patients with prostate cancer.

3. Nuclear-Structure-Based Serum Markers of Prostate Cancer

**Robert Getzenberg, PhD, Professor, Urology, Pharmacology and Molecular Science
Johns Hopkins University (Baltimore, MD)
*PCF Competitive Award Recipient***

Dr. Robert Getzenberg from Johns Hopkins has developed a test for EPCA-2, a cancer-specific protein molecule. Getzenberg proved EPCA-2 was made in cancer cells, not normal cells. He has presented results related to the characterization of an EPCA-2 test in post-prostatectomy patients, and showed that patients with potentially curative surgery revert to a zero EPCA-2 value.

Studies evaluating EPCA-2 as a marker for disease recurrence, and as a biomarker to inform treatment efficacy, are ongoing. We are hopeful that Johns Hopkins will be successful in developing EPCA-2 into a robust progression biomarker, and in licensing its EPCA-2 technology in the near future for development of a commercial clinical lab test. We also hope this test will be available to patients within two years of Johns Hopkins obtaining a commercial partner.

Key Findings:

- Unlike micro-RNAs, or DNA tests like gene fusions, EPCA-2 is a prostate-cancer-specific biomarker protein.
- Antibodies have been produced to develop a lab test to detect EPCA-2 being released from early prostate cancer.
- Applications of an EPCA-2 test include: (1) risk stratification for prostate cancer detection and, (2) identifying individuals with elevated PSA levels and/or positive digital rectal exams that will have a high probability of a positive biopsy of the prostate.
- EPCA-2 might be useful as a biomarker of disease progression and for measuring therapeutic response.

4. Detecting Circulating Prostate Tumor Cells with Microfluidic Device

**Gerhardt Attard, MD, PhD, Senior Clinical Research Fellow
Royal Marsden Hospital (London, U.K.)
*The Susan and James Blair - PCF Young Investigator Award Recipient***

**Howard Scher, MD, Chief, Genitourinary Oncology Service
Memorial Sloan-Kettering Cancer Center (New York, NY)
*Competitive Award Recipient
PCF Challenge Award Recipient 2008-2011
Charter member and leader of the PCF Therapy Consortium***

**Daniel Haber, MD, PhD, Director
Massachusetts General Hospital Cancer Center (Boston, MA)
*PCF Challenge Award Recipient 2008-2011***

In some patients, tumor cells circulate prior to metastasis. A novel microfluidic device, developed by Drs. Daniel Haber and Mehmet Toner of Massachusetts General Hospital Cancer Center, enables a blood test to isolate circulating tumor cells (CTCs). Although it is not yet approved for clinical use, it may eventually play a key role in numerous aspects of cancer diagnosis and treatment, including detecting and evaluating metastatic disease, selecting and individualizing initial surgical and medical therapies, monitoring disease progression, detecting the occurrence of therapy-induced mutations and the consequent development of resistance, and understanding the fundamental biology of metastasis.

Current detection methods successfully detect CTCs in only half of samples known to contain them. The new device consists of approximately 80,000 micro posts covered with antibodies against the epithelial cell adhesion molecule (EpCAM), permitting them to selectively bind CTCs. The bound cells are visualized with fluorescent staining and optical microscopy. The device has been used to detect CTCs from prostate, lung, breast and gastrointestinal cancers. Staining techniques for specific molecules, such as prostate specific antigen (PSA), provide reliable confirmation of the source of the CTCs.

The PCF is funding the next phase of research being conducted with the microfluidic CTC chip developed by Drs. Haber and Toner. Using the device, Drs. Rick Lee and Matthew Smith at the Massachusetts General Hospital Cancer Center, are directing clinical trials to analyze CTCs in prostate cancer patients. The research seeks to validate prostate cancer applications for CTC analysis similar to those already shown for lung cancer. The clinical trials include correlating CTCs with borderline or rising PSA levels, pathological and histological analysis, and the likelihood of post-operative recurrence, rapidly measuring therapeutic responses, detecting the development of resistance and genetic changes, such as translocation and androgen receptor mutation, and understanding the disease process to identify diagnostic markers and novel therapeutic targets.

This technology provides a minimally invasive technique for early detection of tumors and metastasis. A single cancer cell can be isolated from over a billion red blood cells in a routine blood test using this new convergence of microelectronics, material sciences, and molecular biology. We call this approach at the PCF a “liquid biopsy” for prostate cancer biomarkers. We have an enormous amount to learn about the strengths and limitations of these liquid biopsies and how to apply them to routine daily care of patients. Analysis of CTCs can indicate the type of cancer, its aggressiveness, and its susceptibility to particular treatments. New biotechnologies allow a single isolated tumor cell in a patient to be analyzed for genes that can help predict response to drugs before they are used.

Also, it may be possible to measure remissions earlier using liquid biopsies than to use conventional CT scans and other radiology tests. Although the absolute number of CTCs in the blood so far has not correlated well to tumor size, variations in CTC levels over the course of treatment do correlate with X-ray evaluations of progression and remission, providing an important and responsive means of monitoring the efficacy of standard or experimental regimens. In fact, ongoing research at Memorial Sloan-Kettering Cancer Center (Dr. Howard Scher) and the Royal Marsden (Dr. Gerhardt Attard, the Susan and James Blair - PCF Young Investigator) is validating CTCs in a Phase 3 clinical trial as a surrogate for survival. These studies employ an FDA-approved CTC device produced by Veridex, a J&J company. The microfluidic CTC chip should prove to be a major

advancement in this technology with great increases in sensitivity and specificity of detecting these important cells.

Key Findings:

- Microfluidic CTC chips is a new technology for measuring circulating tumor cells (CTCs).
- CTCs are detected in the blood from patients with a variety of solid tumors.
- In lung cancer, this test provides a noninvasive serial monitoring method for clinical response, and for the detection of the molecular cause for drug resistance.
- In prostate cancer, it is being tested as a progression biomarker and as a surrogate endpoint for survival in clinical trials.

5. Genomic Alterations and Prostate Cancer Risk

**William Isaacs, PhD, Professor of Oncology, Urology
Johns Hopkins Medical Institutions
PCF Gene and Family Consortium Awardee**

William Isaacs, PhD, has led a global consortium of geneticists in the discovery of genomic alterations that predict prostate cancer risk. Most recently, a panel of ~20 genomic changes that can be detected in a blood test, distinguish prostate cancer risk from the population of approximately 6% to over 50% when the individual also has a strong family history. This assessment could be used for a 20-year-old person with a family history, and genomic alterations, to predict risk for prostate cancer at a much older age.

As significant as risk prognosis might be, this analysis still does not inform the individual or his physician if the resulting prostate cancer will be clinically meaningful in his lifetime.

A recent and hopeful development from a Johns Hopkins' study is the identification of a DNA-based genomic alteration associated with aggressive prostate cancer. Although the association is relatively weak and not yet a proven diagnostic for lethal prostate cancer, the hope is that ongoing analysis of large patient populations (thousands) will reveal additional genetic markers associated with aggressive disease. These hypothetical markers, in conjunction with the previous risk markers and family history, hold the promise of identifying those individuals appropriate for intensive clinical surveillance for aggressive prostate cancer.

Key Findings:

- The ability to identify genomic alterations in a biopsy with DNA sequences that are associated with prostate cancer clinical behavior is rapidly advancing.
- DNA markers are available today that differentiate individuals at low and high risk for developing prostate cancer in their lifetimes.
- More than 20 genomic alterations have been associated with prostate cancer risk.

The Promise of New Prostate-Cancer-Specific Biomarkers

The development of new clinical laboratory tests will ultimately deliver a better diagnosis for every patient that is capable of predicting aggressive cancers and identifying those that will never take the life of a patient. These enhanced tools for monitoring disease progression will save countless lives and spare countless men from unnecessary treatment.

PCF is working daily with the PCF-funded Therapy Consortium to have the patient samples in place in order to rapidly test these new biomarkers as they become available for validation. In this way PCF should be able to reduce the time to realization of better tests for patients. A secondary use for some of these biomarkers will be to assess patient response to experimental treatments during clinical investigation. Progression biomarkers (such as CTCs) are already being tested in clinical trial surrogates at this writing. If successful, the surrogate would inform investigators months, if not years, earlier of positive effects in certain patients of new anti-prostate cancer medicines.

The field is advancing rapidly and we are monitoring progress weekly in our research briefings and journal clubs. We will provide updates on a regular basis on progress made in the above biomarker research projects. Also, we will formally review how much progress has been made in the last year - along with the most recent data - in our 2009 Scientific Retreat (September 24-26, 2009).

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