

NOVEMBER/DECEMBER 2014

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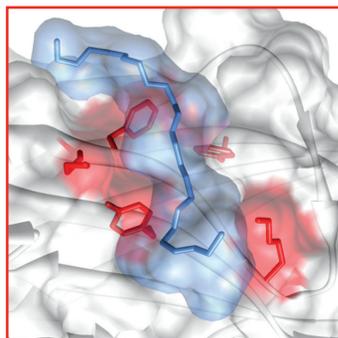
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Defining Distinct Molecular Classes of Prostate Cancer

Christopher E. Barbieri, MD, PhD, alternates seamlessly between his clinical practice in the Department of Urology at NewYork-Presbyterian/Weill Cornell Medical Center and scientific investigations in his laboratory at Weill Cornell Medical College. It is the best of both worlds, providing him with perspectives on prostate cancer that inform both the direction of his research and decisions on treatment strategies for his patients.

“I care for patients with clinically localized prostate cancer, and my research in defining distinct molecular classes of the disease dovetails closely with my clinical practice,” says Dr. Barbieri, who recently joined



In this SPOP structure image, the protein that SPOP binds to is depicted in blue. Newly discovered amino acid mutations in prostate cancers are shown in red.

Source: *European Urology*, October 2013

the full-time faculty of the Department of Urology after completing both his urology residency and urologic oncology-focused fellowship within the Department. “Prostate cancer is a tremendously variable disease. There are many patients with clinically localized prostate cancer with indolent disease that will never threaten their health. Then there are many patients with rapidly progressive disease that leads to metastasis and death. The clinical and pathologic parameters we as

physicians currently have to use do not adequately distinguish these groups of patients. We have incomplete information on who has low risk disease and who has aggressive disease.”

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A Comprehensive Program for the Management of Peyronie’s Disease

Peyronie’s disease (PD) was first described more than 250 years ago, but until recently, no effective treatments were available except for surgery. Indeed, most men and many practitioners have limited knowledge of PD and its often-disconcerting

“There are a number of evidence-based interventions that we can offer in the management of Peyronie’s disease.”

— Dr. Peter J. Stahl

presentation of penile curvature. Today, however, help is available through a range of medications and medical therapies, in addition to surgery.

“Peyronie’s disease is a connective tissue disorder of the penis – either triggered by a traumatic event or occurring spontaneously – in which

penile shape changes begin to occur that can include curvature, loss of length, penile indentation, and other shape variations,” says **Peter J. Stahl, MD**, Director of Male Reproductive and Sexual Medicine in the Department of Urology at NewYork-Presbyterian/Columbia University Medical Center. “PD can be a very functionally and psychologically devastating disease for men. Here at Columbia, we are able to offer a comprehensive approach to the diagnosis and non-surgical and surgical management of Peyronie’s disease.”

PD occurs when plaque develops from scar tissue that forms in the tunica albuginea, the tissue that comprises the walls of the paired erection chambers within the penis, most commonly on the top or bottom. The plaque reduces the elasticity of the tissues and flexibility of the penis during erection, and as the plaque continues to build, the

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Defining Distinct Molecular Classes of Prostate Cancer (continued from page 1)



Dr. Christopher E. Barbieri

In 2013, Dr. Barbieri co-authored a review article titled “The Mutational Landscape of Prostate Cancer,” which was published in *European Urology*. The article covered relevant literature on recent studies of somatic alterations in prostate cancer with a focus on common genomic alterations that form the molecular basis of prostate cancer, their functional significance, and the potential to translate this knowledge into patient care.

“Advances in sequencing technology have resulted in an explosion of data regarding the mutational events underlying the development and progression of prostate cancer, verifying that heterogeneity is the norm in this disease,” reports Dr. Barbieri. “With the advances that have been made in cataloging these genomic alterations, prostate cancer has the potential to transition from being a poorly understood, heterogeneous disease with a variable clinical course to being a collection of homogenous subtypes identifiable by molecular criteria.”

This is, in fact, the goal of Dr. Barbieri’s current research endeavors. “Under the microscope prostate cancer may look very similar, but with the advent of genomics and being able to look closely at the DNA and RNA level of these cancers, we’re seeing

very clear differences in and distinct classes of prostate cancer,” says Dr. Barbieri. “With that in mind our hypothesis is that these distinct classes of prostate cancer may have very different effects on patient prognosis and be associated with distinct risk profiles.”

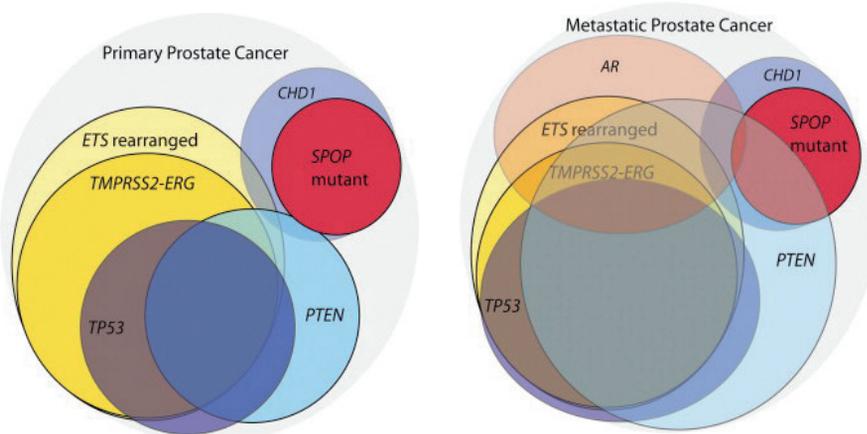
Dr. Barbieri’s research took a major step forward in 2012, when he and his colleagues at Weill Cornell Medical College, in collaboration with a team of researchers from the Broad Institute of MIT, identified a specific molecular class of prostate cancer. “We discovered mutations in the SPOP gene in 10 to 15 percent of human prostate cancers,” notes Dr. Barbieri. “This gene hadn’t

Dr. Christopher E. Barbieri was first author on a paper published in *Nature Genetics* in 2012 that exposed SPOP mutations in prostate cancer and the recurrent molecular abnormalities that came along with them.

been well-known previously to be a cancer gene. What is interesting about these prostate cancers is that they lacked many of the genetic abnormalities we find in other prostate cancers, for example, the fusion gene *TMPRSS2/ERG*, which is the most common abnormality in prostate cancer. They also largely lacked deletions in a tumor suppressor called *PTEN*, which is also very common in prostate cancer. But they did have specific genomic abnormalities that are found much less commonly in other prostate cancers. So the package of these abnormalities, the SPOP mutations, and the other genomic deletions really supported this being a distinct biological entity and raised the possibility that SPOP-mutant prostate cancers will have specific biomarkers for diagnosis, specific effects on patient prognosis, and possibly be amenable to specific management strategies and targeted therapy.”

The SPOP mutation became the primary focus of study in Dr. Barbieri’s laboratory and, since that time, he and his colleagues have established transgenic mouse models of SPOP mutation in the prostate to study their effects on prostate tumorigenesis. They have now defined the prevalence and associated molecular characteristics of SPOP mutations in demographically diverse cohorts of prostate cancer spanning Caucasian, African American, and Asian ethnicities; geographic sites in North America, Europe, Asia, and Australia; PSA-screened and un-screened populations; and multiple stages of disease. “SPOP mutations are present in all cohorts at similar frequencies with distinct associated molecular features,” explains Dr. Barbieri. “This supports the SPOP-mutant class of prostate cancer as relevant across diverse patient cohorts.”

Molecular Classification of Prostate Cancer



Systematic sequencing studies continue to add data allowing the definition of molecular subclasses based on mutations and copy number aberrations. Diagram indicates the overlap and mutual exclusivity of different molecular alterations in prostate cancer.

Source: *European Urology*, October 2013

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A Comprehensive Program for the Management of Peyronie's Disease *(continued from page 1)*

penis will curve or bend, causing painful erections and making sexual intercourse painful, difficult, or impossible.

Affecting some 2 to 8 percent of the population, PD can develop in men in their 30s and sometimes younger, with its prevalence increasing with age. While the etiology of PD is unknown, it is generally attributed to acute trauma during intercourse, athletic activity, or an accident, chronic injury, and autoimmune disease. Occasionally it can be triggered by prostate cancer surgery or treatment. PD can be associated with Dupuytren's hand contracture, and has a higher incidence in individuals with a family history of PD.

"While the historical view among many urologists has been that there is little that can be done for PD other than to wait and see what happens, there are a number of evidence-based interventions that we can offer in the management of Peyronie's disease," says Dr. Stahl. "Our singular goal is to restore functional erections and a patient's confidence and self-image."

Diagnosis is based on the clinical history and acquired penile shape changes that are pathognomonic for Peyronie's disease, says Dr. Stahl. On physical examination the plaque can be felt, and the patient's history combined with findings from the physical exam form the diagnosis.

"One important step that we do is an objective assessment of deformity and erectile function using duplex Doppler penile ultrasound in order to establish a baseline for the patient and understand the severity of the disease," says Dr. Stahl. "This enables us to assess the patient's erectile function so that we can make informed, personalized decisions about treatment."

The assessment involves an intracavernous injection of a vasoactive agent to induce a rigid erection; physical examination of the erect penis using a goniometer to measure angle; and then an ultrasound scan of the penis to identify the plaque and its characteristics. "In particular we want to identify whether or not the plaque is calcified, which has prognostic implications; and then to measure velocities within the cavernosal arteries to determine the vascular health of the penile blood vessels," says Dr. Stahl. "That becomes important because the management of Peyronie's disease is different for people with normal erections as compared to individuals with erectile dysfunction."

Dr. Stahl explains that Peyronie's disease can cause significant distress for patients, leading to a diminished self-image and a decrease in sexual desire. Many patients develop erectile dysfunction. "It's important to separate the people with true physical problems causing erectile dysfunction from those who have what we call psychogenic ED," he says. "Often once you address the Peyronie's disease, clinical erectile function can improve."

"When we have objectively established the degree of penile deformity, the angle of curvature, and penile vascular erectile function, we then tailor therapy to each individual patient based on their goals," continues Dr. Stahl. "We offer a combination



Doppler ultrasound showing a large Peyronie's plaque



Dr. Peter J. Stahl

of four treatment modalities – medication, physical therapy, intralesional therapy, and surgery. Intralesional therapy involves direct injection of medication into the Peyronie's plaque. Penile plication is a straightening surgery that carries a very low risk of erection problems, but does shorten the penis slightly; grafting procedures actually provide penile length, but risk causing erectile dysfunction."

In the early phase of PD, Dr. Stahl focuses on the use of oral and injectable medications to control pain, and physical therapy with a penile traction device. "This approach requires the patient to wear a penile stretching device three hours a day. Though onerous, it is a good primary treatment for patients who prefer a conservative approach, as well as an adjunctive treatment for patients pursuing other therapy."

In December 2013, Xiaflex® (collagenase clostridium histolyticum) became the first and only FDA-approved treatment for PD in men with a palpable plaque and a penile curvature deformity of 30 degrees or greater at the start of therapy.

"Xiaflex has demonstrated efficacy in randomized placebo-controlled trials," says Dr. Stahl, noting that Columbia is one of the busiest centers for Xiaflex administration in New York. "This medication is only approved for the stable phase of Peyronie's disease. We are using it in select cases in the early phase of PD, but generally we're waiting until the disease is stable for several months before prescribing."

With the approval of Xiaflex, says Dr. Stahl, there has been greater public awareness and attention focused on Peyronie's disease. "More people are coming forward and seeking out treatment," he adds. "With Peyronie's disease, there are a lot of objective and very personal, patient-driven factors that play a major role in decision making. As a center that is committed to taking care of men with this disease, we have the interest, time, and expertise to assess all of those factors and work with the patient to form the most effective treatment plan."

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Defining Distinct Molecular Classes of Prostate Cancer (continued from page 2)

Using pre-clinical models, cells derived from patient tumors with these alterations, as well as more conventional cell lines, Dr. Barbieri and his team are seeking to define a number of questions: What are these mutations doing potentially to cause prostate cancer? How do they work? How do they specifically collaborate with the other genetic alterations seen in prostate cancer? Why are they mutually exclusive with some of the more common abnormalities found in prostate cancer, and what does that mean in terms of therapy?

Their endgame, of course, is to define specific pharmacologic and other interventions that will be able to target prostate cancers with these mutations specifically. “We are early on in this aspect of our research,” says Dr. Barbieri. “Because I have a foot in both worlds, I know what’s going on clinically for prostate cancer patients. One of the tremendously exciting aspects of this field is that in the past several years, the number of new agents that have been approved for patients with advanced prostate cancer has skyrocketed from one or two to nearly a dozen. The fact is if you have a dozen therapies that all work, they’re probably not going to all work the same for all patients. There will be some patients in which some of these new therapies are going to work much better than others. Figuring out who should get which of those new therapies, alone or in combination, and even in what order they should get them, is going to be a very interesting avenue of this research over the next years.”

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For More Information

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