Prostatepedia[1]

[1]expert insight + advice

Genomics

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In this issue....

I am especially excited about our April issue. Genomics offers multiple ways to improve prostate cancer treatment. We are only at the beginning of the genomics revolution.

I am well aware, though, that many of our readers may not have a sufficient scientific background to fully understand the power of this way of looking at cancer.

The key insight is that *gene expression* determines a cancer cell's behavior. Before the genomics revolution, we tried to predict cancer behavior based on appearance under the microscope—i.e. Gleason grade or imaging techniques. This approach has had its successes but is far from perfect. Instead of inferring behavior from appearances, genomics looks directly at the genes that drive behavior.

Genomics for prostate cancer is most advanced for newly diagnosed low to intermediate risk disease. We have several competing commercial products; the three most widely used are Decipher, Oncotype, and Prolaris. All three look at the expression of multiple genes. The pattern of expression of these genes has been shown to correlate with a cancer's future behavior.

I have been particularly interested in a next generation test called the Decipher Grid. It dramatically expands the number of potentially important genes tested. This includes genes that may predict responsiveness to radiation, hormonal therapy, and some chemotherapy agents. Time will show Decipher's Grid's usefulness.

When a specific gene mutation is known to drive the growth of a cancer, it is possible to develop drugs that selectively kill cancer cells that have that mutation. This process has already revolutionized lung cancer treatment.

For prostate cancer, we now have only a few examples. In several conversations this month, doctors mention DNA repair mutations BRCA2 and ATM. These mutations are commonly linked to breast and ovarian cancer. A class of drugs called the PARP inhibitors are effective treatments for ovarian and (to a lesser extent) breast cancers containing these mutations. When these mutations are inherited, they are associated also with an increased risk of aggressive prostate cancer.

While the frequency of BRCA2 mutations is low at diagnosis, the incidence increases as prostate cancer advances. Several studies show that 25-35% of advanced prostate cancers contain mutant BRCA2 or ATM. One Phase II clinical trial reported a greater than 80% response to a PARP inhibitor.

Other genes important in aggressive prostate cancer include TP53, PTEN, and RB1. However, no drugs are clinically available to target cells where the function of these genes has been altered or eliminated. TP53 and PTEN have selective drugs in preclinical and clinical testing.

The take-home message is that genomics is already improving the treatment of newly diagnosed prostate cancer and offers hope for better treatments for advanced disease.

Charles E. Myers, Jr., MD Pp1

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Guest Commentary
Oliver Sartor, MD

We can divide genomics into two different categories. The first category is germline genomics, which is the DNA with which you're born. It's clear that about 12% of people with advanced prostate cancer will have alterations in their inherited DNA, in particular in genes involved with DNA repair. Most common of these alterations are BRCA2. There are a variety of others that are somewhat prevalent, including ATM, CHEK2, and BRCA1. There are others that are more rare.

The implications of these germline mutations are significant for the patient: in certain configurations they may predispose a cancer to be sensitive to certain therapies, such as PARP inhibitors or platinum-based chemotherapy or (rarely) immunotherapy. There is more complexity, but knowing the germline mutation helps the informed clinician make decisions. In my practice, we test all patients with advanced prostate cancer for these germline mutations. (A National Comprehensive Cancer Network guideline suggests the same approach.)

These germline mutations represent the DNA with which you're born. That DNA is going to have repercussions if also mutated in your family members. Men who have some of these DNA repair mutations have an increased risk of prostate cancer. In addition, there is a small increased risk of pancreatic cancer and male breast cancer for those with some of the germline mutations. Around 30% of men with BRCA2 will be diagnosed with prostate cancer in their lifetime, but that cancer is more likely to be aggressive if diagnosed.

> *"We are in the middle of a revolution, but the parts and pieces are not yet clear."*

With regards to females, it's particularly important. Females with DNA repair defects are more likely to have breast and ovarian cancer. Female with DNA repair mutations, in particular BRCA1/BRCA2, ought to consider having their breasts or ovaries removed at an appropriate time. Prophylactic surgery has been demonstrated to be potentially life-saving for those individuals. The risk of breast cancer may be as high as 70% and the risk of ovarian cancer may be as high as 40%.

Thus, for these germline mutations there are implications for treatment and implications for the patient's family.

We should be doing prostate cancer screening earlier in men with these DNA repair defects for prostate cancer; we should be doing biopsies at a PSA of 3 or higher, and perhaps even lower, for younger men known to be at risk. Starting screening at age 45 has been suggested by some.

In addition to germline genomics, we need to also talk about somatic genomics. Data indicates that about 60% of individuals who have a DNA repair germline mutation are likely to have another second genetic mutation occur within their tumor. In addition, many of the tumors can acquire an alteration in their tumor DNA even when the germline is normal.

Taken together, about 20 to 25% of men may have DNA repair mutations in their tumor's DNA. That makes them particularly sensitive to certain therapies such as the PARP inhibitors, as I mentioned earlier, or platinum chemotherapy. When you have two DNA repair mutations in the same cell, the likelihood of response to these agents appears fairly high.

There are also other DNA defects of considerable interest, such as alterations of the mismatch repair genes MSH-2 and MSH-6. When these alterations do occur, there is a potentially increased probability of responding to immunotherapy such as the new PD-1 inhibitors.

Overall, the guiding light today in genetics in my practice is to look at both the germline DNA and the tumor DNA. I choose to look at the tumor DNA circulating free DNA (cfDNA) tests, in particular the Guardant Health assay. The ability of other assays to corroborate the Guardant Health findings is not yet clear. There is clear data to indicate that different assays give different results, but nevertheless, I think in the early exploratory phase we're in now, it's important to begin to test patients in order to better understand their genomics and hopefully guide us towards better therapies. This will happen part of the time but certainly not all of the time.

There is more to the story of prostate cancer genetics. We've looked at androgen receptor mutations that can have implications for a response to Androgen Receptor directed therapy, such as Xtandi (enzalutamide), Zytiga (abiraterone), and Erleada (apalutamide). We're dissecting a number of permutations that occur. It's a complex scenario, because very few men have only one mutation. Most have multiple mutations. And in most cases, these mutations are not targetable with current therapies. This is very important for people to know. Everybody thinks if they get a genomics test that means they've got a treatment. It's not the case. Many times we get the genomics results and find that there are no known treatments we can use for that man's particular alteration.

That said, there is a subset of men who will have informative genomics while many more people will have non-informative genomics. There is a final issue I'd like to discuss. There is currently a bit of a debate amongst physicians over the utility of PARP inhibitors such as Lynparza (olaparib) as compared to platinum chemotherapy. But it is noteworthy that platinum-based chemotherapies are inexpensive compared to PARP inhibitors. This does not require a clinical trial. (Most men will access PARP inhibitors through a clinical trial, although sometimes insurance companies are willing to try.)

As it turns out, neither the platinum-based chemotherapies nor the PARP inhibitors will be effective forever, so we do need strategies to manage patients after PARP inhibitors or platinum-based chemotherapies fail. Currently, that space is unexplored. We have to gather much more data before we can make conclusions about those with underlying DNA repair defects who have failed platinum-based chemotherapy or PARP inhibitors.

This is an area of active and important investigation that represents a conundrum for many patients today. I've got a patient right now going through this. We're debating what to do next. I've tried to be as honest as I can when I say, "I don't know what to do, but we've got to try something."

We are in the middle of a revolution, but the parts and pieces are not yet clear. For some, understanding tumor genetics at the current level is helpful. For others, it is perplexing and expensive. Pp

Felix Y. Feng, MD
Genomics + Personalized Medicine

Dr. Felix Feng is a physician-scientist at University of California, San Francisco (UCSF) keenly interested in improving outcomes for patients with prostate cancer. His research centers on discovering prognostic/predictive biomarkers in prostate cancer and developing rational approaches to targeted treatment for therapy-resistant prostate cancer. He also sees patients through his prostate cancer clinic at UCSF.

Prostatepedia spoke with him about how genomics is personalizing medicine for patients.

Why did you become a doctor?

Dr. Feng: I became a doctor because my family has a strong history of cancer. Unfortunately, I learned the repercussions of cancer at an early age. All four of my grandparents passed away from some form of cancer. My father has successfully overcome three different cancers. Just last year, my sister, unfortunately, passed away in her 40s from cancer.

Before ever becoming a doctor, I was part of many patients' families. I saw it strongly from the patient side and decided that if I was going to commit my life to studying something, it was going to be cancer.

So then your journey is really personal.

Dr. Feng: Very personal.

How is genomics changing how doctors decide who needs treatment for prostate cancer and who doesn't?

Dr. Feng: Our field is in an exciting time in terms of advances in genomics and prostate cancer. For the vast majority of the past few decades, prostate cancer treatment has been selected and optimized outside of genomics. We've had a number of breakthroughs in the last few years that have suggested that a large part of prostate cancer treatment in the future may rely on genomics.

The most important example of this is the use of PARP inhibitors in men with prostate cancer that have DNA repair alterations, and most commonly, alterations in the genes BRCA1, BRCA2, and ATM. Including this example, we have three examples in the context of metastatic prostate cancer where genomics is actively being used to personalize therapy.

A study from Dr. Johann de Bono's group at the Royal Marsden in the United Kingdom first demonstrated that patients who have DNA repair alterations have responded particularly well to the PARP inhibitor Lynparza (olaparib). In a follow-up study, which was run out of the University of Michigan, Drs. Maha Hussain, Arul Chinnaiyan, and I confirmed these findings in the context of a randomized trial. It's clear that using PARP inhibitors for patients with DNA repair alterations is one example of using genomics for personalized medicine. There are a number of different companies now exploring a variety of trials trying to get PARP inhibitors FDA approved as a therapy for patients with metastatic castration-resistant prostate cancers.

A study reported by Dr. Johann de Bono at the European Society for Medical Oncology Conference about two years ago demonstrated that patients with prostate cancers in which a gene called PTEN is inactivated responded well in a randomized trial to an AKT inhibitor. That is now being evaluated in a Phase III trial.

Another use of genomics to advance medicine is in cancers with alternations in a class of genes called mismatch repair genes, which have been shown to confer sensitivity to various immunotherapies. That represents an approved syndication across all cancers, not just prostate cancer.

In the localized prostate cancer setting, there are two genomic classifiers based on RNA expression that help identify patients with low-risk prostate cancer who are more likely to progress to more aggressive disease. This may be used to determine which patients should be followed with active surveillance. The two classifiers that are most commonly utilized in this setting are Oncotype DX by Genomic Health and Prolaris by Myriad.

"There are now a number of strategies that use genomics to personalize medicine."

In the context of higher risk patients treated with surgery, there's a classifier called Decipher made by GenomeDX Biosciences. That has been shown across very large numbers of patients to be a prognostic of metastatic progression after radical prostatectomy. Already, that classifier has been incorporated into ongoing clinical trials to select which patients with aggressive disease should be candidates for treatment intensification.

Can genomic classifiers be used to select specific patients for specific therapies?

Dr. Feng: My team has helped develop two of the first clinical-grade classifiers predictive of their responses to specific therapies. One is a biomarker panel called PORTOS, which stands for Post-Operative Radiation Therapy Outcomes Score, and may be useful in predicting response to post-operative radiation therapy—those treated

"Many of the clinical trials being developed nowadays incorporate genomics."

with radiation therapy after radical prostatectomy. PORTOS predicts specifically which men will benefit from radiation therapy. We validated its performance in a manuscript published in Lancet Oncology two years ago.

More recently, we've applied a genomic classifier utilized in breast cancer to prostate cancer. It's called PAM50 and is used to determine which women with breast cancer should get hormone therapy after surgery. It turns out that these molecular subtypes of breast cancer also exist in prostate cancer. Specifically, we found that there are luminal A, luminal B, and basal subtypes of prostate cancer.

When we look at which patients are most likely to hormone therapy, our initial data suggests that it's the luminal B patients who have the most aggressive disease and who also benefit from hormone therapy. We did all of these studies in large retrospective cohorts, but because we wanted to validate this prospectively, we are about to initiate a trial in the context of a national clinical trial called NRG-GU006, run by the NRG Oncology Clinical Trials Group.

With NRG-GU006, we stratify patients by their PAM50 molecular subtype. These are patients who have been treated with radical prostatectomy and have had biochemical PSA recurrence. These patients are stratified by PAM50 status, and then they are randomized to standard therapy —which is salvage radiation alone— or salvage radiation plus short-course Erleada (apalutamide), which is a next generation anti-androgen.

From all of these examples, you can see that, across different contexts— from active surveillance to the more aggressive, locally advanced prostate cancer to metastatic prostate cancer, there are now a number of strategies that use genomics to personalize medicine.

Can genomics predict who will have certain side effects?

Dr. Feng: There have been a number of studies that have used single nucleotide changes within DNA sequences, called single nucleotide polymorphisms (SNPS), to predict who will be most likely to experience side effects from radiation therapy for cancer.

In general, the signal from these toxicity studies has been weaker than the signals from biomarkers that predict responses to particular therapies, like the ones that I mentioned earlier. This may be reflective of the fact that radiation acts through a variety of mechanisms, so any single biomarker may not work well. Even when you cluster biomarkers, it may not account for the heterogeneous manner in which radiation causes a biological effect.

What should patients know about how genomics is impacting treatment?

Dr. Feng: Many of the clinical trials being developed nowadays incorporate genomics. We have clinical grade assays to look at

"Genomics will have a major role in prostate cancer going forward."

genomics. We have strong biological rationale for why certain genomic biomarkers may identify subsets of patients who can respond to specific therapies. Because genomics is routinely used to personalize treatment in the context of diseases like breast cancer, colon cancer, and melanoma, it's only expected that genomics will have a major role in prostate cancer going forward.

Will incorporating genomics into clinical trial design accelerate the speed of innovation?

Dr. Feng: I think it will. If you look at metastatic castration-resistant prostate cancer, for example, a number of therapies have been approved by the FDA over the last decade for those patients, including agents like Zytiga (abiraterone) and Xtandi (enzalutamide), next generation taxanes, Provenge (sipuleucel-T), and Xofigo (radium-223). All of these agents extend survival by just a few months. This is invariably what happens when you treat prostate cancer as one disease entity rather than a variety of different entities that are governed by different genomic events.

As we become better at selecting therapies based on a patient's genomic events, we should see longer response times to available therapies and those currently being developed. Fp

Eric Klein, MD
Genomics + Active Surveillance

Eric A. Klein, MD, is an international leader in the biology and management of prostate cancer. Dr. Klein serves as Chairman of the Glickman Urological & Kidney Institute at the Cleveland Clinic.

Prostatepedia spoke with him about how genomics impacts active surveillance.

Why did you become a doctor?

Dr. Klein: I don't really know. I never remember wanting to do anything else.

Even when you were a little kid?

Dr. Klein: When I was in first grade, I missed a month of school because I had what they thought was rheumatic fever. My pediatrician came to see me a couple times a week. That doesn't happen so much now.

No. It doesn't.

Dr. Klein: I suspect that's had some influence because my parents really respected him.

But I can't articulate it for you. I never wanted to do anything else. It was not an intellectual decision. It's just what I wanted to do. I was born wanting to be a doctor.

What kinds of genomic tests are patients likely to encounter today?

Dr. Klein: Before PSA came along, half the men who were newly diagnosed with prostate cancer had metastatic or other incurable disease. The most common operation we did was bilateral orchiectomy, because that was the only androgen deprivation therapy available. There were no drugs available that were safe. (We had estrogen, but it wasn't safe.)

Five years after PSA was introduced, 95% of patients presented with early stage disease. We believed back then that every cancer that was detected needed to be treated. We believed that every cancer had metastatic, or lethal, potential and we treated all of them.

As the population got screened every year, we culled out the aggressive cancers in the population. Then we started detecting new cancers in patients who hadn't been screened before, cancers that were so early that, after a while, we recognized that they probably didn't need to be treated. The whole idea of active surveillance came along.

Active surveillance has been around in a substantive way for about 15 years now. In the beginning, our decision-making on who was eligible for active surveillance was pretty rudimentary. It was based on what we saw on prostate biopsy, which we know under-sampled the prostate. Even though we were doing biopsies by ultrasound, we knew that we were missing some people who weren't eligible for surveillance. But if we found the right patient who had just a minimal amount of Gleason 6 cancer, we put them on surveillance.

As large numbers of patients who were being followed carefully got older, we realized that we were missing some patients who had higher-grade cancers and probably weren't good candidates for surveillance in the first place. And a small percentage of the patients who started out with low-grade disease progressed while they were being followed to the point where they needed to be treated.

Again, that was all based on biopsy. Now it's based on imaging with MRI, which allows targeted biopsy and makes it less likely that a high-grade cancer will be missed.

We developed genomic tests to improve our ability to select the correct patients for surveillance and to know when to pull the trigger, meaning when to treat those who have progressive disease. I started working with Genomic Health on Oncotype around 15 years ago, when active surveillance was just starting. Many people, me included, were reluctant to put patients on surveillance because we didn't know anything about the biology of the tumor.

We only knew about the histology, or the microscopic anatomy of cells and tissues, of prostate cancer and we weren't sure exactly who was eligible. We weren't sure how to follow them and we didn't know when the right time was to pull the trigger with curative treatment. We were still over-treating patients, so the development of genomic tests was motivated by two things: 1) to increase our confidence that we were doing the right thing for patients and not harming them using, for the first time, a direct measurement of tumor biology; and 2) we wanted to develop a biologic tool that would help us decide when to pull the trigger when the tumor required treatment.

Active surveillance is well established now. Many more patients go on surveillance. In Sweden, 90% of eligible men go on surveillance. There is not a lot of population-based data in the United States, but the data that exists suggests about 40% of eligible men in the United States go on surveillance and the number is growing.

There is a lot of variability in individual practices. MUSIC in Michigan is a collaborative group of 13 urologic practices who have agreed to share their data. Across the 13 practices, about 50% of patients go on surveillance. However, there is a huge range of willingness to put patients on surveillance among practitioners within each practice. The lowest number that go on surveillance in one practice is 25% while another practice has about 70% on surveillance. There is still plenty of opportunity to increase our confidence and put more men on surveillance. That is really the goal.

My goal in 2018 is to only treat lethal cancers, or cancers that have lethal potential, and put everybody else on surveillance. That is how I approach patients now. The first question I ask is: *is there some reason why this patient is not a candidate for surveillance?* Surveillance is always the first choice, so I want to make that decision based on the biology of cancer.

These new tests have revealed that histology tells us some things about the biology of a tumor, but not everything about the biology. I'm trying to get the world to change their thinking. My most recent presentations always begin with a slide that says: *Think Biology, Not Histology*. We have maxed out all the information we can get out of what a pathologist sees when they shine a white light under the microscope on the tumor.

What we've learned with these tests is that about 5-10% of low-grade Gleason 6 cancers, which we would otherwise consider for surveillance, have molecular features of high-grade cancer. They are probably not good candidates for surveillance, even though pathologists have correctly called them Gleason 6 cancers.

In a small number of cases, molecular changes that are submicroscopic turn a low-grade cancer into a high-grade cancer before the pathologist can detect it. An MRI probably can't see those molecular changes either. I rely on these tests as an adjunct to what we learn from biopsy and imaging to make the correct decision about whether or not he should go on surveillance. These tests measure the biology of the tumor in a way that we have not been able to measure before.

If you have a high-grade cancer you don't need a genomic test. You know you need to be treated. But if you have a little bit of low-grade cancer, you don't know with absolute certainty whether surveillance is safe or not..

There are probably some patients with intermediate risk cancer, Gleason 3+4s, who lack molecular features of high-grade cancer even though they have some pattern 4 in their biopsy. We can use these tests to identify them and selectively put them on surveillance.

How do the individual tests differ from each other?

Dr. Klein: These tests measure the expression of genes in prostate cancer. That's what they're designed to do. They predict the likelihood of your having higher-grade cancer or cancer that penetrates the rind around the prostate (called extraprostatic extension), or cancer in the lymph nodes or seminal vesicles. These tests predict that better than biopsy or plain old Gleason grading. This gives us a leg up in deciding who is a good candidate for surveillance.

If your biopsy only shows Gleason 6, but you actually have higher-grade cancer in the prostate, or you have some cancer that's through the rind or in the seminal vesicles, you're not a good candidate for surveillance. We know that from decades of doing radical prostatectomies. These patients are at highest risk for progression and that's what these tests measure. They also tell us whether a pure Gleason 6 cancer is one of the 5-10% that has molecular features of high-grade cancer.

These are biopsy-based tests. For example, if a patient has a biopsy that shows Gleason 6 cancer and otherwise favorable features, such as a PSA below 10, and a PSA density below 0.15, we wonder whether he's a candidate for surveillance. We always do a confirmatory test after a first biopsy.

Decipher (http://deciphertest.com/) can also be used after the prostate has been removed to help decide on the need for additional treatment.

A genomic test like this is appropriate in some patients. An MRI of the prostate is appropriate in others. Sometimes it's appropriate to get both. We don't have enough experience to know which is the best test for which scenario, although I have some ideas about that. Then, once we confirm that the patient has a low-grade cancer that lacks molecular features of high-grade cancer, we feel confident in putting him on surveillance.

The results can do two things. They can confirm that the patient is a candidate for surveillance. Sometimes they can convince a reluctant patient that surveillance is the right thing. We don't want to over-treat people who have low-grade cancers that aren't going to kill them because the side effects of treatment are worse than the likelihood of his dying of cancer. Sometimes, the results can convince a physician that surveillance is the right thing. If you look at the criteria for putting people on surveillance, it's mostly patients who have just a minimal amount of cancer–low-grade cancer, a Gleason 6 on a biopsy.

We published a study in the *Journal of Urology* recently that showed that even among patients with high-volume Gleason 6 cancer in multiple cores—four or five remove cores—many have no molecular features of high-grade cancer. In the past, they haven't traditionally been considered good candidates for surveillance, but based on the biology of their tumor, they are good candidates for surveillance.

You may have someone who has a couple of cores of low-grade cancer, maybe a PI-RADS 4 lesion on MRI. You're not sure if they're a good candidate for surveillance or not. If a genomic test confirms the absence of molecular features of high-grade cancer, you can put the patient on surveillance. That is the kind of information that genomic tests provide. They have their nuances.

Oncotype and Decipher are good for patients with very low, low, and favorable intermediate-risk disease. Prolaris is best validated for patients who have intermediate-risk disease. It doesn't have good discriminatory value for low grade cancers. Generally, they all measure gene expression and they're all are used in the same way.

These tests help determine whether or not someone is a candidate for surveillance. At the moment, we don't use these tests based on biopsy to determine which treatment to give a patient, but that's coming. Post-prostatectomy, Decipher can help tell us that.

There are challenges to active surveillance. Say we put someone on surveillance and he starts out with 1 core of Gleason 6 cancer. A year later, he is re-biopsed and has 3 cores of Gleason 6 cancer. We don't know whether that's true biologic progression that requires treatment, if all that Gleason 6 cancer was there in the beginning and was just not sampled by biopsy, or if the patient grew some new Gleason 6 cancer that doesn't have any biologic potential.

This isn't established yet, but I believe we can use these tests for what I call serial biologic monitoring, meaning you biopsy patients a year or three apart. These tests, for the very first time, allow us to measure true changes in biology as opposed to just changes in what we see on biopsy, which may underestimate what's going on in the prostate. This is a new paradigm.

Another common scenario is a man who has a low-grade cancer on initial biopsy (1 core, Gleason 6) and a year later has a little bit of Gleason 3+4 with 5% pattern 4 and 95% pattern 3. In the past, that would always trigger treatment. But it's my belief, based on what we've learned from these tests, that this is probably not correct. Many of those men can still stay on surveillance.

How commonplace are these tests?

Dr. Klein: Any physician can order these tests. There is not a lot of market data out there, though on a recent Twitter poll about 25% of urologists said they are routinely ordering these tests deciding how to manage surveillance. The market share is roughly equal between them.

My understanding is that each company is doing about 15,000 tests a year. If you look at it that way, 45,000 men are getting these tests now. That means a fair number of men are starting to make decisions based on biology and not just histology.

Will a local urologist or oncologist necessarily know what to do with the information?

Dr. Klein: No. We're in the midst of a genomic-based paradigm shift and people are still educating themselves about it. That whole field isn't limited just to surveillance. There is now genetic testing available to determine if you've inherited a gene that predisposes you to prostate cancer.

If a man reading this is in a rural area where this type of information is just now getting to his local medical community, does it make sense for him to get this testing on his own and then find someone who can interpret the results?

Dr. Klein: There's a difference of opinion there. I'm a believer in these tests. I think that having the most information you can get about someone's cancer most often leads you to the right decision, so I encourage people to get them. There are a lot of nonbelievers who haven't been convinced. A little bit depends on how aggressive your own personal philosophy is about putting men on surveillance.

If you're a urologist who doesn't put many men on surveillance because you're uncertain about the biology, the selection criteria, and how to follow people, then you certainly should get comfortable and use these tests because they help you make all of those decisions.

If you're someone who already puts 90% of your Gleason 6 cancers on surveillance, then you might not find the same utility in these tests.

If I were a cancer patient facing a decision about getting treatment, I would want my doctor to have as much information as possible about my cancer to make an informed decision and get it right the first time. That's always the best chance for cure; it's always the most cost-effective way to manage things.

Isn't it true that a lot of men who technically can stay on surveillance choose to go off and get treatment?

Dr. Klein: Yes. Around 50% of men who start on surveillance end up being treated. There are a variety of reasons for that. A lot of it has to do with PSA anxiety.

For men with a little bit of low-grade cancer, most of their PSA comes from their BPH, not from their prostate cancer. We know that PSA from BPH fluctuates over time. As you get older, your PSA goes up because the prostate gets leakier. As you get older, your prostate gets bigger, so your PSA goes up. There's a lot of difficulty interpreting PSA when the biopsy hasn't changed any. That's because PSA is not a direct measure of cancer biology, but these tests are. That's where I think they can be useful.

A recommendation from a physician can also trigger treatment. A physician may see that you had 1 core of Gleason 6 a year ago and now you have 4 cores of Gleason 6, so they assume that must be progression. But the actual number of patients who progress in grade is probably pretty small—10% or less. We can use these tests to reduce the likelihood that someone is going to come off surveillance.

Some of it is just surveillance fatigue. We put men through a lot to stay on surveillance. There is worry involved. There are repeated MRIs. There are repeated biopsies. Patients get tired of that.

Do these tests help give men confidence that this is an appropriate choice for them?

Dr. Klein: Yes. For the first time, these are direct measures of individual tumor biology. That's what we want to base our decisions on, not only on what we see under the microscope. There are several patterns of care studies published that show that men who have these tests are more likely to go on surveillance and stay on surveillance than men who don't.

In my talk that begins with a slide that says *Think Biology, Not Histology*, the last slide reads *Treat Biology, Not Histology*. That's the paradigm shift that we need. These are first generation tests that aren't perfect, but they are better than histology alone and are only going to get better through additional iteration.

How does Decipher work?

Dr. Klein: Decipher was initially marketed on prostatectomy specimens for patients who've already had surgery. You harvest the tumor from the excised prostate and measure a 22-gene expression signature. With Decipher, you can predict the likelihood that someone is going to recur and get metastatic disease within five to ten years. That's very solid data and can help you select the patients at highest risk of recurrence who might benefit from additional treatment, such as adjuvant radiation therapy.

The folks at GenomeDx have developed something called the GRID, which measures a much broader array of biology. Oncotype measures 12 cancer-related genes and 5 housekeeping genes. Prolaris measures 30-some odd genes that measure only cell cycle progression. Decipher on biopsy or prostatectomy measures 22 genes, but the GRID measures 1.4 million bits of biological information. It gives you a wonderful insight into what the biology of the cancer is. We're just starting to tease out from the GRID different molecular subtypes of prostate cancer that behave differently and that respond to treatments differently.

GRID is still used for research purposes, but it's going to form the basis of a number of prospective tests that allow us to determine on biopsy if someone won't respond to radiation therapy and is absolutely better off being treated with surgery, or if they might respond to radiation. Post-prostatectomy, GRID will help determine which medication they might respond to, whether they're going to be hormone sensitive or not, and whether they should be treated with chemotherapy. That's precision medicine, the personalized medicine era coming along now in prostate cancer.

What about people who've already had a prostatectomy? Would you say the same thing to those men?

Dr. Klein: That's a different scenario. I would only order Decipher post-prostatectomy in patients who have pathologic features that suggest they're at risk of recurrence where I might consider adjuvant radiation therapy. That's really what it's designed for.

If you had Gleason 6 or 7 prostate cancer that was organ-confined without extraprostatic extension with negative margins, negative seminal vesicles, and negative lymph nodes, you probably don't need Decipher.

If you have someone with extraprostatic extension and a focal positive margin, and your inclination is to follow that patient closely and radiate them when their PSA goes up or to give them adjuvant radiation, then Decipher helps answer an important question: whether or not that patient needs treatment and when.

There are some people, even with seminal vesicle invasion which is generally considered a very poor prognostic factor, who have very low Decipher scores and are not at high risk of recurrence. They can probably avoid additional treatment, at least in the short term.

Are these tests routinely covered by insurance companies?

Dr. Klein: Some insurance companies pay for them routinely. Medicare covers these tests for NCCN-defined very low, low, and and favorable intermediate-risk cancer.

How expensive are they when not covered?

Dr. Klein: The list prices are in the thousands of dollars. Most of the companies are discounting the cost

of the test if insurance doesn't pay, or they will accept whatever insurance covers, so that varies by company.

Is there anything else patients should know about these genomic tests?

Dr. Klein: I've been doing this for almost 40 years. It's maybe the most exciting time to be a prostate cancer doc because of these new tools. I liken it to the invention of smartphones. Smartphones put information at our fingertips that makes our lives better. These tests do the same thing.

For the first time, they give us a clinically useful window into the biology of the cancer. That is going to revolutionize how we treat patients with prostate cancer.

For patients with metastatic disease, it's possible to take a piece of tumor, send it off to the lab, have it sequenced, and get a result back in a couple weeks to see if there are specific genes driving the growth of the tumor. In a small percentage of patients (currently 5-10%), there are drugs available to target and turn off that gene. These have been shown to make tumors regress and to prevent them from coming back, which makes people live longer. Not everybody who is treated that way is cured, but those are significant advances over standard ways of treating everybody with shotgun chemotherapy.

And these are first generation tests. The iPhone that I carry on my belt has more computing power than the technology that sent the astronauts to the moon. These tests are only going to get better. That's why this is exciting. Pp

John L. Gore, MD
Does Decipher Change Treatment Choices?

Dr. John Gore is a clinician, surgeon, researcher, and educator specializing in urologic oncology and general urology at the University of Washington.

Prostatepedia spoke with him about how Decipher changes the way doctors treat men with prostate cancer.

"It's not a common event."

Why did you become a doctor?

Dr. John Gore: My initial vision for my life was that I was going to be a lawyer. Then I found that I really enjoyed my experiences while interning at the hospital. That brought about an application to medical school. I think being a doctor offers a chance to have a daily meaningful impact, which is a unique part of the job.

How did you end up working in urology?

Dr. Gore: Urology is a specialty that very few people enter medical school thinking that they want to do. In part, most people are like I was and don't even know about the specialty. I don't have any doctors in my family. The only doctor I knew was my own pediatrician. I just assumed I was going to be a pediatrician.

But I really enjoyed surgery. I enjoyed being in the operating room. I just really enjoy the generic construct that someone has a problem and I have the tools to fix it.

Urology is an interesting hybrid. Most surgeries have a homolog in internal medicine. For example, there's cardiothoracic surgery and cardiology. There's colorectal surgery and gastroenterology. We don't really have that in urology. We do a lot of chronic disease management. We do a lot of long-term follow-up of our own patients. It is, in many ways, a hybrid of internal medicine and surgery, which is really cool.

What is Decipher?

Dr. Gore: Decipher is from a family of genomic tests. In general, it tries to look at some of the alterations in people's genes associated with cancer or its progression. Decipher attempts to create a panel of genes associated with the likelihood of a cancer coming back. It takes that panel of genes and integrates it with clinical information to calculate the risk of developing spread of cancer to sites that could be detected clinically, like the bones or the lymph nodes, within five years after prostate cancer surgery.

When is a man likely to encounter this test? After that initial biopsy when he is first diagnosed? After his prostatectomy?

Dr. Gore: The most common scenario would be after surgery. If a man has his prostate removed and the pathology shows that he has a cancer that by all accounts seems to have been successfully treated with the surgery, Decipher may not be the right test for him.

If he has some high-risk features—his cancer is potentially encroaching on the shell of his prostate, he has a positive surgical margin, or there is involvement of the seminal vesicles that sit behind the prostate—then he might benefit from Decipher. That way we can ask if—in addition to knowing that he had some high-risk pathology eatures—he appears genomically to have a high-risk cancer?

What do the results look like? Do they change how a man is going to be treated post-surgery? How?

Dr. Gore: The actual report that a patient or doctor gets tells them the probability, or percent risk, that he will have clinical metastases within five years of having his prostate removed for prostate cancer. In general, those numbers tend to be in the single digits to low teens. It's not a common event. For most people, prostate cancer surgery successfully treats their cancer. That is why this is best used on higher-risk individuals.

In our study, we looked at a cadre of patients who were either found to have high-risk features at the time of their prostate cancer surgery, or now their PSA is subtly rising after going to zero after surgery. Those patients should potentially have more aggressive treatment.

We showed that if a patient had the Decipher test, physicians' recommendations changed. If your Decipher results showed a lower risk score, your doctor was more likely to recommend observation. Patients with a higher risk Decipher score were more aggressively treated. They were recommended to go ahead and get additional radiation to the area where their prostate was removed, rather than just active surveillance.

"Decipher is from a family of genomic tests."

The bottom line is that Decipher changes how men are treated?

Dr. Gore: Yes. We have some follow-up data we just presented at the *American Society of Clinical Oncology, Genitourinary* meeting in February that showed that those treatment recommendations were actually followed 80% of the time.

You said only men who are high-risk should really be tested. Not everyone getting prostate cancer surgery needs a Decipher Test?

Dr. Gore: That's right.

Is Decipher widely accepted in the medical community? If a man in rural Minnesota goes to his local urologist or local community oncologist, will he likely be offered the Decipher Test? If not, should he ask his doctor to order it?

Dr. Gore: I think it's definitely worth requesting it. One thing that has come up is insurance payer coverage, not just for the Decipher Test, but also for other tests like it. The bar that some of these companies have to cross to get their test approved is fairly high.

Some insurance companies are asking if the test not only changes treatment for patients. The trial they're looking for will compare patients who got the Decipher Test with patients who didn't to see if the decisions that were made impacted cancer outcomes. If, for example, your Decipher results say you're high-risk, and you get radiation based on that information, was that the correct decision? The challenge is that prostate cancer is immensely slow-growing. Even when it's high-risk, even when it's aggressive, we're talking about clinical outcomes that take years and years to manifest. It imposes an irrationally onerous burden to prove that these tests are the right thing.

You could wait 10 years to find out if the treatment decisions were correct. Meanwhile, time is passing and these men need to make choices…

Dr. Gore: Absolutely.

"Patients with a higher risk Decipher score were more aggressively treated."

Is there anything else you think patients should know about the Decipher Test or its impacts on treatment choice?

Dr. Gore: We were mainly interested in Decipher's impact on treatment recommendations, but we also looked at decisional conflict and decisional anxiety. *Does Decipher make me feel better about the decision that I'm making?* We found that patients who got the Decipher Test had more decisional certainty. Decipher was associated with significantly reduced decisional conflict. And men had less concern about their prostate cancers coming back if their Decipher results suggested they were low-risk.

That's a pretty big deal. Stress about treatment choice is a significant factor for many men.

Dr. Gore: Absolutely.

Especially because there is so much controversy within the medical community over what the right path may be.

Dr. Gore: I think one of the things that people talk about when they talk about prostate cancer is how hard it is to make a decision about what treatment is right for you. That's just the first decision. If you are unfortunate, you may have many other decisions to come. There are a lot of really challenging decisions men face in their life trajectory with prostate cancer. Pp[1]

David J. VanderWeele, MD, PhD: Can Genomics Impact Your Treatment?

Dr. David J. VanderWeele is an Assistant Clinical Investigator in the Laboratory of Genitourinary Cancer Pathogenesis at the National Cancer Institute. He is particularly interested in investigating the progression of clinically significant prostate cancer.

Prostatepedia spoke with him about how genomics impacts patient care.

Why did you become a doctor?

Dr. VanderWeele: Physicians come to the job through a number of ways. For me, it was both an interest in biology in general and in cancer biology specifically. I really enjoyed learning in undergraduate school, and later on in training, how cancer represents a normal biological process gone awry.

Of course, many people also have a family member who helped inspire their choice, either directly or subconsciously. My mother had breast cancer; I'm sure that was part of my internal motivation and interest in oncology.

How did you end up specializing in prostate cancer?

Dr. VanderWeele: I was interested in genitourinary oncology—prostate cancer, bladder cancer, kidney cancer, and testicular cancer—because there is a wide range in the natural history of those diseases and how we treat them. I became especially interested in prostate cancer in part because some prostate cancers are very aggressive and others are more indolent. The first step of managing prostate cancer is assessing the risk of the disease and not just treating all cancers the same way.

What is genomics, and how does it differ from genetics?

Dr. VanderWeele: Typically if you're talking about genetics, you're talking about an individual gene or a small set of genes. When you refer to genomics, you're referring to all the genes or a very large set of genes. Genomics usually refers to the genes–the DNA sequence. But sometimes genomics is also used to refer to when those genes get expressed (as RNA), or to other changes to the DNA that don't change the DNA sequence (also called epigenetics).

What do and don't we know about why some men develop curable or indolent prostate cancers while some develop widely lethal diseases?

Dr. VanderWeele: A lot of effort has been put into trying to learn more about the genes you inherit from your parents and how that influences the likelihood that you're diagnosed with cancer. Most of that effort has been unable to identify which alterations in your genes make it more likely that you will get an aggressive versus an indolent cancer.

As many of your readers probably know, many people get indolent prostate cancers. In fact, many autopsy studies have looked at patients who have died of other reasons and have never been diagnosed with prostate cancer. Once men reach their 70s or 80s, it looks like more than half of men develop prostate cancer. Of course, those are relatively slow-growing cancers.

The most information that we have now is that men who come from families with breast and ovarian cancer syndrome appear to be more likely to get cancer and more likely to get aggressive cancer. These involve BRCA1, BRCA2, and other DNA repair genes in a similar pathway. Though there aren't FDA-approved therapies yet, there are trials suggesting that these patients are also more likely to respond to certain therapies approved for breast and ovarian cancer.

This is a pretty small subset of all the men with prostate cancer, but the percentages increase with any kind of measurement of aggressiveness. If you look at people with localized cancer, that percentage increases if you have high-grade cancer versus low-grade cancer. The percentage increases if you compare people with advanced castrate-resistant prostate cancer to those with localized cancer. If you look at the length of time between a man's diagnosis and when he dies, that rate increases significantly the shorter that time is. That is just looking at three of these genes, BRCA1, BRCA2, and ATM.

If you look at a broader number of these DNA repair related genes, it looks like ten to twelve percent of all patients with castrate-resistant prostate cancer harbor a mutation that they inherited from their parents. It seems likely that for most of those patients, that inherited gene contributed to their prostate cancer.

That has led to some debate about how often we should test for mutations in these genes. Is that a high enough number that we should test everyone with castrate-resistant prostate cancer? Should we still rely on family history to provide guidance for which people should be tested?

Is it really expensive to test those men? Why wouldn't you just go ahead and test?

Dr. VanderWeele: Depending on how you do it, testing costs have come down quite a bit.

But when you're testing for genes that could potentially be passed on to your offspring, or that siblings or other family members may have inherited, there are implications for your other family members, not just for you.

Some members of your family may definitely want to know that information and think that more information is better. Others may feel that if they find out that they harbor that gene mutation, they will just feel like they're waiting for the other shoe to drop. It's not information that they'd want to know.

Generally, we advise people to get counseling to help them think through some of these issues before getting tested for genes they've inherited from their parents.

Do we know why some men respond to certain drugs and therapies and others don't?

Dr. VanderWeele: There's a lot of interest in that. There has been some progress made in terms of identifying the biomarkers that might suggest which patients are more likely to respond to which types of therapies. At this point, however, most patients still get treated with most therapies.

There are some genetic biomarker-driven therapies that look like they're on the horizon. Patients with mutations in BRCA2, ATM, and related genes are more likely to respond to a type of therapy called PARP inhibitors, which are currently approved for patients with ovarian or breast cancer, but not yet for prostate cancer.

There was a single Phase II study that showed that patients who had loss of a specific tumor-suppressor gene called PTEN are more likely to respond to a certain type of targeted therapy.

There are larger ongoing trials to demonstrate that these are indeed predictive biomarkers for response to these therapies.

There are companies like FoundationOne and GenomeDX that look at the molecular features of a man's cancer. Are those tests useful? What do they tell a patient?

Dr. VanderWeele: The FoundationOne test looks for mutations, deletions, or amplifications of specific genes that are relevant for a wide array of cancers. There are a lot of companies offering this type of sequencing. Many hospitals offer their own version of it. A FoundationOne type of test can tell you if you have a mutation in BRCA2 or ATM. They should also be able to tell you if you have a deletion in PTEN. When they detect a mutation is present, however, generally they are not looking to determine if you inherited those changes from your parents versus the mutation being present only in the tumor cells.

These genetic tests are more popular in other types of cancers, because for prostate cancer there aren't yet any FDA-approved therapies that would be given based on the results of these tests. These tests will become more popular as we make progress in demonstrating the benefit of these specific therapies and in our ability to predict which patients are most likely to respond.

If a patient reading this gets one of those tests, is it likely that his doctor is going to know what to do with the results? Will the results actually impact his treatment?

Dr. VanderWeele: There are probably a small number of patients who will have a result that will directly impact their therapy. At this point, the way that it would impact therapy is that it might suggest that they should find a clinical trial testing a specific type of drug.

I see.

Dr. VanderWeele: There are also other commercially available prostate specific genetic tests, like the one performed by GenomeDX, that are mostly aimed at men with localized prostate cancer who are trying to decide how aggressive their therapy should be. Typically, this means

whether they should pursue active surveillance or get surgery or radiation.

Sometimes these tests are also used to determine if a patient should get radiation after undergoing a prostatectomy or if he should just continue to follow PSA numbers. The prostate specific gene expression tests are RNA-based tests, which are a little different. They measure the levels of expression of a few specific genes. Tests like FoundationOne look for mutations, amplifications, or deletions of genes—which means they are DNA-based tests.

Tests like Decipher are more widely used now, right?

Dr. VanderWeele: Yes. They're probably used mostly by urologists. My sense is that how often urologists order those tests and how heavily they rely on them versus other ways to predict the risk level of the prostate cancer varies quite a bit from urology practice to urology practice.

All of this is exciting and still emerging, but most of these tests aren't ready for primetime, correct?

Dr. VanderWeele: It's fair to say the use of these tests is still evolving, but at this moment, they can influence a man's decision about how to manage his cancer.

Commercial tests like Decipher and Oncotype DX are commercially available, and there is a lot of retrospective data that has been analyzed with those tests. Tests like those offered by FoundationOne are well established for some other cancer types, but still emerging for prostate cancer because we don't have any FDA-approved therapies for prostate cancer that depend on the results.

There is one other type of mutation that can predict responses to certain types of therapy. People who inherit mutations from their parents in Lynch syndrome associated genes, which we usually associate with colon cancer, are also more likely to develop other types of cancers. It looks like prostate may be one of those other types of cancers.

You can develop a mutation in those genes even if you didn't inherit it from your parents, just in the process of your prostate cancer developing. Those who have mutations in these genes tend to have a really high number of mutations in their tumors.

It looks like those patients are also more likely to respond to some of the immune-based therapies that have been successful for other types of cancer, but that don't look like they're especially helpful on their own for prostate cancer.

Last year the FDA approved a checkpoint inhibitor immunotherapy that wasn't specific for a disease, but instead specific for patients harboring these Lynch syndrome-related mutations. This was the first time the FDA gave a tissue-agnostic approval for cancer therapy.

Are you talking about Keytruda (pembrolizumab)?

Dr. VanderWeele: Yes. Most of the patients who have these mutations and are likely to respond to Keytruda (pembrolizumab) have colon cancer or endometrial cancer. It looks like maybe around three percent of patients with castrate-resistant prostate cancer may harbor these types of mutations. Of those three percent, it could be that many will respond to these checkpoint inhibitor types of therapies.

As for PARP inhibitors for patients with BRCA2, ATM, or other DNA repair gene mutations, if these therapies become FDA-approved, then we'll talk about not just treating patients with advanced late-stage prostate cancer, but also about moving the therapies up to an earlier disease state.

Nearer to diagnosis?

Dr. VanderWeele: Yes. Or if you undergo surgery, but have a high risk disease and a significant risk of it coming back. Or if you don't have any evidence of metastases showing up on scans, but your PSA has started to rise after you got surgery or radiation. One complicating factor for doing genomic testing for patients with cancer only in the prostate, rather than a metastasis that can be biopsied, is the degree of heterogeneity in the prostate. Because we know that there is a lot of heterogeneity in prostate cancer, the question becomes: *what is the best way to test for these genomic biomarkers?* Whether or not you see a mutation in these genes may depend on which part of the prostate tumor you're sampling and analyzing.

It looks like genomics is one of the more exciting fields in prostate cancer.

Dr. VanderWeele: Yes. It's a question of *when* PARP inhibitor therapies will be approved, especially for people with BRAC1, BRAC2, or ATM mutations, not *if*. Pp

Clinical Trial: Eliezer Van Allen, MD Genomic Profiling + Metastatic Prostate Cancer

Dr. Eliezer Van Allen, Assistant Professor of Medicine at Harvard Medical School, a clinician at Dana-Farber/Partners Cancer Care, and an Associate Member at the Broad Institute of MIT and Harvard, focuses on computational cancer genomics, using new technology in precision medicine, and resistance to targeted prostate cancer therapies.

Prostatepedia spoke with him about the Metastatic Prostate Cancer Project (www.mpcproject.org), a nationwide genomic research study for men with advanced or metastatic prostate cancer.

Why did you become a doctor?

Dr. Van Allen: An engineer probably would've been closer to what I had imagined. Medicine was, in some sense, an accident.

When I went out to college at Stanford University in the late 90s, I studied something called Symbolic Systems, which is a mix of computer science and a bunch of other coursework. Many of my friends from that era, who studied the same things, stayed in Silicon Valley and are now software engineers, computer scientists, and whatnot.

While I was pursuing this degree of study, some of my friends worked on creating Camp Kesem, a camp for kids who have or had a parent with cancer. (It seemed like a cool thing to do, I'd do some good, and learn something.) We had the first camp in 2001 with 37 kids. I was lucky to be a counselor.

I say, very genuinely, that that was a life-changing experience. It really exposed me to a humanistic side of medicine, which I really hadn't seen up to that point. It also exposed me to the world of cancer and how cancer touches not just patients but their whole families. That pushed me to pursue medicine, and cancer medicine in particular. It was a seminal life experience. It's cool to see how that program has grown both locally and nationally. There must be hundreds of Camp Kesems at this point.

How did you get involved with prostate cancer?

Dr. Van Allen: While in medical school and residency, I met patients who had prostate cancer. I was really struck by them. I'd meet them in the hospital, some when they were very sick and often times with advanced cancers. A lot of the prostate cancer patients appeared to be very different

from each other and from all the other cancer patients I saw. In part, this was because the treatments were so different than those given for other cancer patients across the board. It was just so striking.

Even back then, when I didn't understand the details and nuances, I noticed that some men seemed to bounce back from any kind of cancer-related illness and live for many years. Others, who were often on the younger side, would have catastrophic advanced disease, terrible side effects to the treatments, and would die quickly. That puzzled me.

I got to know a lot of these guys while working at the Veterans Administration Hospital in San Francisco. I just felt a very symbiotic bond. I don't know how to explain it. There's some sort of unwritten connection with these men that resonated with me.

I took that with me into my continued training as an oncologist, both clinically and as a computational biologist. As a person with a computer science background who started to build a career at the intersection of cancer genomics, prostate cancer, clinical medicine, and the emerging space of cancer data sciences, this particular puzzle became very exciting to explore, for both humanistic reasons and the emerging scientific reasons.

What do we know already and what would we not *know about cancer genomics?*

Dr. Van Allen: Quite a few large-scale genetic studies defined the genetic landscape of both primary prostate cancer, which is local to the glands, and metastatic prostate cancer, which is spread outside the gland. It is often metastatic cancer that kills people. These studies looked at the genomes of cancers and performed computational analyses to sift through all of the molecular data to find the patterns associated with cancer. As much has been done, there are still many things that we don't understand.

There are a few things missing from our first draft of a map for the genetics of local and advanced prostate cancer that we hope to address with the Metastatic Prostate Cancer Project (https://mpcproject.org/home). One: deep resolution. From our prior work, we know that learning from 100 patients is good, 1,000 patients is better, and 10,000 patients will give even better resolution. That level of detail will be incredibly valuable for identifying genetic targets that might be relevant for new drugs and treatments.

Second: the vast majority of what is known about prostate cancer comes from genetic studies dominated by Caucasian men. In parallel, we know that African-American men who get prostate cancer will oftentimes get it at a younger age in more advanced settings and are less responsive to treatment. The Metastatic Prostate Cancer Project, which is accessible to anyone with a computer, is one mechanism to make the information more representative. We're working closely with our patient advisory council to expand the network and the participation rate in non-Caucasian patient populations.

Third: we have genetic maps, but they don't really have any context, meaning that more often than not we don't know what happened clinically to the patients who have been genetically profiled. One of the most important questions in the prostate cancer world is: *why do patients respond or not respond to some of the newer drugs that we use for men with advanced prostate cancer?* If we think there's a genetic cause for that, either from the tumor or from the patient's inherited DNA, then linking the genetic data with the clinical data is mission critical. Right now, that can't really be done in any meaningful way because we don't actually have the clinical data. With this project, we have permission to get the clinical data in addition to the genetic data, and we ask those seminal questions to guide the next wave of therapeutics in this disease.

> *"We're trying to create a resource that anyone could use."*

What is the Metastatic Prostate Cancer Project?

Dr. Van Allen: The Metastatic Prostate Cancer Project is a patient-driven research initiative whereby we researchers partner directly with patients to dramatically expand the scope of our understanding prostate cancer genetics. We try to fill in all of the missing gaps that are currently a challenge in our field. Hopefully, we'll learn what drives advanced prostate cancer, how to treat it more effectively, come up with new drugs, and understand the differences between more indolent cancers and those that progress in the metastatic setting. Essentially, I want to answer the questions I had during my initial clinical observations way back when.

You say you want to partner directly with the patients. How does that disrupt the normal clinical trial process? Normally, patients would access trials through their doctors?

Dr. Van Allen: Exactly. That's what I've done during my postdoctoral training and in my junior faculty stage. That's what we all do: we devise the research project, write a bunch of protocols and consent forms, and get them approved in our hospitals. Then we rely on the doctors and research teams to approach patients. They consent their patients to the studies that are already defined and set in stone. We use that to research. That's obviously been a driving force for many modern discoveries. It's a remarkable thing.

And that's how we have to lay the first genetic maps of prostate cancer and cancers in general. This project flips genomics on its head.

We've been working with prostate cancer patients to build a project with, by, and for men with advanced prostate cancer, their families, caregivers, and loved ones in order to resonate with patients. We are creating a mechanism such that patients can consent without leaving their home and participate without necessarily living near an academic medical center. This helps expand the scope of what we were able to learn in new ways.

"That puzzled me."

A couple of years ago, while trying to define the genetic maps of local and advanced prostate cancer, we launched the first of these patient-driven projects at the Broad Institute in metastatic breast cancer. Using social media, patient outreach, advocacy partners, and patients themselves describing what it means to participate in these projects, that study enrolled over 4,000 women and men with metastatic breast cancer. Given that we're thrilled when the average study to define the genetic maps of prostate cancer enrolls 100 patients over the course of years, if not decades, that number in such short time is remarkable. As we developed that project, I immediately thought of prostate cancer.

Rather than doing a top-down research project whereby we start with an idea in a researcher's head, we go through the hospital and the doctors, and eventually, the patients, we're *starting* with the patients. They're talking directly to the researchers and building up. That is the ethos of this project.

This is not a traditional, academic project whereby we generate all the data, sit on it in our own little groups while we try to make sense of it, and eventually make it available to the larger community. Rather, as soon as we have a nominal amount of data, we make it immediately available to any researcher around the world who wants to use it.

We're trying to create a resource that anyone could use. The first 100 patients with genetic and clinical data have been made available for researchers pre-competitively. We don't wait and publish these results in an academic journal or any other medium first.

Publishing in a traditional academic journal can restrict access for patients. If they want to read to read the results, they have to pay $30 to download the article.

Dr. Van Allen: Exactly.

If someone reading this wants to participate, what do they do?

Dr. Van Allen: If you have advanced prostate cancer, simply go to mpcproject.org. There, the homepage describes what's involved. When you click the "count me in" button, it sends you on what we hope is a very quick journey through a few basic questions. Then, it asks for your permission or consent to participate in this project. There are a few more simple questions after that.

Soon after you register, you'll receive a box that contains a saliva kit that the patient will spit in and return to get their inherited DNA information. Additionally, there's a liquid biopsy kit, which is a vial that you bring to your doctor's appointment to collect a liquid biopsy of your tumor. Then you return the sample to us.

When we receive those materials, we perform genetic profiling and access the medical record data. We de-identify everything to make sure it's private, so nothing is exposed. We build a cohort and learn as we go.

Each step of the process has been vetted, scrutinized, criticized, and modified based on patient feedback such that we hope it resonates with this group. Part of this is actually iterating as we go.

This is a research project. We're not a clinical lab, so at the moment at least, we do not return results to individuals. But we do regularly engage with patients to share aggregate results of anything we learn in real time.

Patients won't have access to the results of their tests?

Dr. Van Allen: Right. Unfortunately, we can't provide individualized results, at the moment at least, because it's beyond the scope of this project. It's something we're very interested in trying to explore. It creates many additional complexities. There is a holy patient/doctor relationship that we want to respect. That being said,often men will ask what's in it for them and ask why would I want to do this?

We try to share aggregate results as regularly as possible. Patients can take those aggregate results, or any sort of interesting findings, to their doctor to consider if it's relevant to them.

Also, it's a beautiful thing to see how patients themselves get when it comes to helping others: *This is for the brothers, the sons, the patients that come after me, and I want to contribute. I want to help solve this puzzle, even if I may not see it in my lifetime.* That altruistic aspect is genuinely great.

They do get to participate.

Dr. Van Allen: Yes. They're just surprised that folks like myself, or anyone in the research world, is even talking to them. But patients are the most powerful people in this world. They have the power to really make these kinds of changes.

I think most people would want to participate if it's easy to do. Are you providing detailed information about the kinds of tests you're running so that if patients wanted to repeat them with their own doctor they could?

Dr. Van Allen: We're doing whole exome sequencing, which looks at all the coding region of the genome on the tumor and the inherited DNA.

We are also piloting sending in liquid biopsies. One emerging technology that's arrived over the last couple of years is the ability to detect circulating DNA that has shed from the tumor into the blood. That is an important advance for this project because most men with metastatic prostate cancer will not have had a biopsy of their tumor at the time of metastatic disease. They may have had a prostate biopsy years, if not decades, before but that tumor from way back when isn't an accurate snapshot of what the tumor is like in the metastatic setting. Detecting a tumor in relative real time using blood is something we're pretty excited to explore as part of this project.

For the men we sequence, we do our best effort to track down their tumor block. We go through every precaution to ensure that we don't exhaust the tumor biopsy and that clinical care comes first. If there's ever a need for it down the road, that's the number one priority. We're exploring how to use these liquid biopsies to help us in this project.

How To Get Involved…

For more information, email Dr. Van Allen at info@mpcproject.org or visit https://mpcproject.org/home

Do you handle the liquid biopsies?

Dr. Van Allen: Yes, it's the Broad Institute.

Can anyone participate? Can non-Americans participate?

Dr. Van Allen: At the moment, we are approved so that anyone from the United States and Canada can participate. Anyone in other parts of the world can complete the survey and provide some of the patient-reported data, but we don't currently have permission to do the subsequent genomic profiling for them.

In our soft launch, we've scanned through self-reported information from almost 200 patients. That has already initiated some ideas for research projects we never would have imagined.

This patient-reported data is quite valuable. Anyone who, at the moment, may not be eligible by virtue of not qualifying from a regulatory perspective for our institutional review board can still contribute to this project in a meaningful way.

A fair number of people travel for medical procedures. If someone travels to the United States for radiation, for example, could they have the samples collected at a United States institution and therefore participate in that way?

Dr. Van Allen: For now, the study can only collect samples and medical records from residents of the United States and Canada. We are actively investigating methods for including international patients.

Is there a fee to participate, or is this free for men?

Dr. Van Allen: Free.

Is there anything else you think men should know about the project?

Dr. Van Allen: We've been concerned about patient interest and openness. In our first project for breast cancer, the social media footprint was quite high. The social media chatter is noticeable and folks feel pretty comfortable expressing their thoughts, feelings, and opinions about their disease. Even though incidents of disease is roughly the same in the United States for breast and prostate cancer, the social media footprint for prostate cancer is the complete opposite.

As we geared up for our soft launch, we were curious to see if we'd end up with the same number of participants, even if we weren't seeing any social media chatter. People don't talk about this disease.

Indeed, on the first version of the saliva kit that we mail out to the patients, *metastatic prostate cancer project was* printed on the box. Men asked us to take that off the box. We didn't understand why. One guy explained: "I don't want the mailman to know I have prostate cancer." It's that kind of challenge we'd like to help overcome. We want to make men feel more comfortable talking about this disease amongst friends, families, and coworkers. We hope this project can be the mechanism to help men open up about it.

It's encouraging that in the first ten days we've accrued an almost identical number of patients as we did with the breast cancer soft launch a couple of years ago. Nobody talks about prostate cancer on Twitter and Facebook, at least in open settings. We're very curious to learn how patients become comfortable talking about this disease and about this project. Pp[1]

Patients Speak
Joel Nowak: Genomics + Metastatic Disease

Joel Nowak is a prostate cancer patient and well-known prostate cancer activist.

Prostatepedia spoke with him about his own patient journey as well as his involvement with the Metastatic Prostate Cancer Project. (https://mpcproject.org/home)

Tell us about your own prostate cancer journey and how you came to prostate cancer activism?

Mr. Nowak: Part of my journey to being an advocate pertains not only to having prostate cancer and recurrence but also to the fact that I had multiple primary cancers. I currently have five different primary cancer diagnoses.

I was treated initially for prostate cancer at the end of 2001. I had a Gleason 3 + 4 with a PSA of only 4. I had surgery. I went back in five years and my PSA went crazy, up into the 80s.

At that point, it was a recurrence. We did a bunch of scans. We identified a couple of lymph nodes in the prostate bed, as well as a very significant and large tumor in my kidney. At that moment, the assumption was that I had a prostate cancer tumor in the kidney and that the kidney had stopped functioning and was basically dead. I had a nephrectomy, which is the removal of the kidney. We found out that it was a different diagnosis: clear cell renal cancer.

Looking back, I see that prostate cancer recurrence saved my life because that's how I found out that I had renal cancer. If it weren't for my prostate cancer recurring, I would not be here today.

I was in my early 50s, so I was fairly young at the time. I knew I was metastatic with prostate cancer and had been diagnosed with another primary cancer. Knowing that I was metastatic weighed very heavily on me. There was no way to use that C-word—cure—which I don't like to use. I looked desperately for people in a similar situation. I refer to it as looking like me, but I don't mean physically. I mean people in their 50s, with a kid in high school, a kid in college, and metastatic prostate cancer that was incurable and possibly terminal.

I found myself becoming angrier and angrier. Not only did I have metastatic cancer, but also I felt very alone in the sense that I couldn't find anybody in a similar situation. I went from one cancer support group to another. Though I lived in metropolitan New York where there are options, I still could never find anybody I could relate to directly, someone with a similar experience. I found plenty of older men who were worried about whether or not they would make it to their grandchild's wedding and things like that, but for me, that had no relevance. I became more isolated, lonelier, and angry.

One night, I was inappropriate with the group leader of one support group. I was overly aggressive and blamed that person for what I perceived as my situation. Instead of reacting to my aggression, the person just sat back in their chair, looked at me, and said, "Why don't you do something about it?"

I went home and discussed it with my wife who tried to stabilize me. "Why don't you," she said. I got angrier at first and just stewed for a while.

It has been 10 years, but when I went to bed that night I thought I was going to die within a few years. It's common for many men with recurrence or metastatic cancer to wonder if they're going to die in a year or two. I felt terrible and angry. I'm not really an angry person, but I had become a very hostile person.

When I woke up the next morning, I decided that I didn't want to live my life feeling that way. I was going to find a way to let go of that anger and do something about it. That's how I got involved with activism.

You decided to channel all the fear, anger, and anxiety into something positive.

Mr. Nowak: Yes. I think that's what it was. I'm not saying that I still don't have moments; I do. And since then, I've had two additional primary cancer diagnoses. One of them was a rare cancer.

But the prostate cancer was the only one that caused that kind of emotional response, probably because that is the only one, so far, that is metastatic.

I spend a lot of time with prostate cancer, but I also work with other cancers—metastatic, advanced, and progressed prostate cancer.

What is the Metastatic Prostate Cancer Project?

Mr. Nowak: This is a joint project between the Broad Institute and the Dana-Farber Cancer Institute.

But what is really more important to me is the researchers who are involved: Dr. Corrie Painter and Dr. Eliezer Van Allen are really committed to what they're doing. They've modeled this project off of a metastatic breast cancer project that they also started.

One of the researchers is a cancer survivor, so they understand what it means to have cancer. Their understanding motivates what they're doing. They're carrying it forward; they're not just doing it because they have a grant.

How did you come onboard with the Metastatic Prostate Cancer Project?

Mr. Nowak: My friend Jack Whelan, who I'd worked with at the American Association of Cancer Research Scientist↔Survivor Program, had a very rare blood cancer. Then one day he surprised me by saying he'd been diagnosed with prostate cancer. I thought he was joking at first.

Unfortunately, his cancer progressed really quickly, probably related to all the treatments he had for his blood cancer. The project staff brought me, Jack, and Jan Manarite in to work on the project.

They asked me to look at their materials and give a patient's perspective. They wanted to know if I found value in the project. They asked me to give them specific feedback and suggestions for improvement. Jack, Jan, and I have also brought in two others. Dr. Van Allen's team has taken all of our suggestions and made the changes.

They also asked us to spread the word, let people know about it, reach out within the prostate cancer community, and help recruit.

What is it about the project that makes it patient-friendly?

Mr. Nowak: The project is patient-friendly because once someone consents and says, "Count me in," the project team does all the work. They send out a package, which we advocates helped redesign, and you just contribute your spit. Then you bring your sample back to the post office or FedEx; it's all prepaid. Spit it and ship it. That's the effort.

We also send out blood vials that are also prepaid. Theoretically, you can walk into a lab and they'll draw your blood for free. Or you can bring the vials to your next doctor's appointment. You don't even have to make a special appointment; just ask them to draw an extra tube.

It's easy.

Mr. Nowak: Yes. It's easy, and it's all prepackaged. Either you or the phlebotomist can just put it into the prepaid package and send it off. You don't have to do much.

Part of the consenting process is the release of the medical records. The project does the sequencing of the blood and saliva, and if applicable, we ask for tissue. There's not a lot of

tissue in prostate cancer, generally, so that was one of the issues I brought up. I wanted to ensure that no one's tissue is used up and withheld from them for the purposes of this research, because you never know when we'll need your own tissue for treatment decisions. We advocates said this was a big issue, so the project will only use a small piece and return it. You need to get it back: you just never know when you'll need it yourself.

You need to look out for yourself.

Mr. Nowak: Yes. It's appropriate to be selfish in this particular situation. The only thing you have to do as a patient is read the consent, discuss it with the appropriate people at the project, sign the paperwork, spit, and bleed. That's all we have to do. Everything else is handled by the project. You don't even know it's happening; it's all behind the scenes.

This is a research project, not a clinical trial, but even with clinical trials everything gets de-identified. That means that your personal information is safe, but you also get no follow-up information. As a patient advocate, I asked what they could do to give some feedback to patients. They were very open to having this conversation, but they are sensitive about over-promising anything. We don't want to mislead anyone.

If we start seeing trends in the data, we will give some feedback. We can't tell individuals that they have gene mutations or not, for example, because their sample was de-identified. But if, hypothetically, we see samples from 300 people with a combination of at least three gene mutations and that 285 people with a particular mutational sequence respond to Xtandi (enzalutamide) but not to Zytiga (abiraterone), then we will give feedback.

But this is exciting. When we start seeing trends or possible trends, the project will release information to people who participate. There will be aggregate data feedback. We'll be able to publish relationships.

It doesn't of course stop me as a patient from going to my doctor and getting sequenced. Probably all of us should be sequenced anyway.

The patient can follow up as he chooses…

Mr. Nowak: Exactly. Then they could say, "I've been sequenced, and I have this mutation." That is just an additional talking point with your doctor from the aggregate data. I'm excited about that. That's going to give some people another thing to consider when deciding between treatments.

Why should men participate? Did you participate?

Mr. Nowak: I did. Jack and I fought over who would be Patient 1. I had respect for Jack, so I told him he could be Patient 0, and I'd be Patient 1. Technically, I'm Patient 2.

Men should participate for a number of reasons. First of all, we have to think about the next generation. My prostate cancer is genetically linked. My father had it. His brother died from it, and his only child, who's older than I, who had been treated. My grandfather had prostate and breast cancers, and my great-grandfather died of prostate problems. Many of us have or are going to have kids, so we should make it a little better for them if we can.

I spend a lot of time working with people and helping them figure out how to have a conversation with their doctor about treatment. Anything that can give us more information and more points of conversation is important.

Aggregate data might help us have better conversations that may help make better decisions going forward.

This is one of those rare research projects where I could possibly benefit directly. As I start going through treatment protocols and so forth, I have no idea where they may find something that works better for me. It's just going to guide my decision-making. Maybe it'll extend my life because I made a better decision thanks to the project.

We also need to understand cancer more generally in terms of genetics and its microenvironments. We need to understand cancer not only as separate diseases. Prostate cancer only describes the organ from which the cancer originates. It doesn't really describe my disease or another's. We need to drill down and understand the type of prostate cancer that one has and how it relates to cancer generally. That is going to guide us in making better decisions.

This type of research is invaluable. There are no risks. There is nothing invasive. The more we understand, the better future research will be, whether for specific treatments or a better understanding of biomarkers, which we have a terrible dearth of knowledge about. To me, it's a no-brainer for us who are going to benefit at no cost.

I hope men sign up.

Mr. Nowak: Yes. That's our goal. Now that we have IRB (Internal Review Board) approval, our next step is to get men signed up.

To participate visit https://mpcproject.org/home

Patients Speak
Steve S:
Genomic Testing

Steve S. talks to *Prostatepedia* about how genomic testing gave him confidence that active surveillance was a safe choice for him.

"I felt like a little bit of a pioneer."

How did you find out that you had prostate cancer?

Steve: I don't remember exactly, but I think I went to the urologist on the recommendation of a doctor who said I should have some PSA tests. I went to the urologist. The urologist ran some PSA tests and said, "They're a little elevated. Maybe we need to run a biopsy," which they did. That was about ten years ago. The biopsy came back with three or four cores indicating cancer with a Gleason score of 6 (3+3), which has remained the same over the last ten years. I think that's what happened.

What kinds of genomic tests did you have and when?

Steve: That happened about five years later. I went to a support group and I heard about genomic testing. My doctor at the time hadn't mentioned anything about genomic testing to me. I said to him that I didn't see any downside in having genomic testing. Why couldn't I have it? He said that he didn't think it would be covered by my insurance and it's not something they had done. I felt like a little bit of a pioneer.

I actually got on the phone with the people at Genomic Health in California and asked how much the test would cost. They mentioned a figure of about

"It confirmed what I was already inclining towards."

$500. I asked, "So that's what I'm going to be charged?" They said, "Probably." They weren't really clear about it. In the end I was never charged.

They sent three results to my physician after a few weeks. Because my physician had never given them instructions as to what risk category he felt that I was in, they sent back three results based on different risk profiles. To this moment, I still don't know exactly which risk profile I fit into.

All three results looked somewhat encouraging to my layperson's eyes. I discussed the results with the doctor at the time and he said, "I think this confirms what we're doing at the moment is right. You can continue on active surveillance, but of course it's your choice." They will always say that….

The results definitely changed your treatment path?

Steve: I was already on active surveillance, although in the first two or three years, I was thinking about some form of radiation therapy. We talked about seeds. We talked about beams. I even talked to a friend a few years older than me who had gone through proton beam therapy and he was very encouraged by his results. My insurance at the time did not cover that, so proton beam therapy came off the table.

I was not thinking about surgery. I was turned off by the idea of surgery, even though they had a DaVinci robot.

Then I got the OncoTypeDX test. I looked at the results with my physician and decided to proceed. It confirmed what I was already inclined towards.

Do you feel like it gave you more confidence in your decision?

Steve: Yes. I think so. I think that's fair to say.

Would you recommend that other men take these tests??

Steve: Everybody has a very different psychological makeup. For example, I've got a brother-in-law who doesn't have prostate cancer, but is very educated on medical matters. He's a smart guy, and so I talked to him about it. He said, "God, if it was me, I would take care of it right away. I'd have that prostate out of there and have peace of mind." I responded with: "I've lost very little sleep over the years about it." That's just my makeup. It doesn't bother me. I've got other things to think about, other things I care about. Health is very, very important. I'm not a complete passenger in this process. That's why it's called *active* surveillance. I'm very careful about going to my doctor's appointments, following up, trying to keep myself educated, and so forth. Would I recommend it to somebody else? Somebody else who has the same psychological make-up that I do? Absolutely. Somebody who is a nervous person, a Type A person, somebody who is likely to lose sleep? Perhaps not.

"I don't see any possible downside to the testing."

I don't see any possible downside to the testing, though. It's another tool for you and your doctor to use to help you make your decisions. Pp1

Merel Nissenberg: Genetic Testing + Counseling

Ms. Merel Nissenberg is the President of the National Alliance of State Prostate Cancer Coalitions, a nation-wide organization comprised of state prostate cancer coalitions dedicated to saving men's lives and enhancing the quality of life of prostate cancer patients and their families through awareness, education, and the development of a public policy network.

She talks to *Prostatepedia* about guidelines for genetic testing in men with prostate cancer.

Much has been written or suggested about the genetic component of some prostate cancers. For example, a family history of prostate cancer can increase a man's risk of such a diagnosis. There have also been articles about the genetic component of certain breast cancers: BRCA1 and BRCA2 have historically been strongly implicated in the familial pathway for that diagnosis. What is more recent is the now more-firmly established connection between certain mutations like BRCA1 and BRCA2 and prostate cancer. However, guidelines for genetic testing in men with prostate cancer have been limited.

Recently, the *Journal of Clinical Oncology* published a special article entitled "Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017" following the Prostate Cancer Consensus Conference held in Philadelphia on March 3-4, 2017. Members of the panel strongly agreed that men should engage in shared or informed decision-making on the issue of genetic testing.

Panel members emphasized the strength of the inherited predisposition of prostate cancer, noting higher risks with BRCA1, BRCA2, and HOXB13 genes. The panel noted that prostate cancer patients with BRCA2 mutations have poor prostate cancer-specific outcomes. We now consider the link between prostate cancer and DNA mismatch repair (MMR) gene mutations to be stronger than we suspected, adding a specific opportunity for treatment. In fact, up to 12% of men with metastatic prostate cancer have inherited genetic mutations, mostly with BRCA1, BRCA2, and ATM. And targeted agents for these specific mutations confer better outcomes for these patients.

The panel concluded that: "Identifying genetic mutations of inherited prostate cancer… has implications for cancer risk assessment for men and their families, for precision treatment of metastatic disease, and is being incorporated into guidelines for individualizing prostate cancer screening strategies specifically for male BRCA1 and BRCA2 mutation carriers."

"Guidelines for genetic testing in men with prostate cancer have been limited."

Unfortunately there are no generally accepted standard guidelines for genetic counseling and genetic testing in prostate cancer, or standards on how to fully interpret results of current panels with multiple gene testing. The information discovered through genetic testing not only informs treatment for the prostate cancer patient himself, but is also an aid to other members of his family, including women who may have a genetic disposition for developing breast cancer. As for the patient, not only does the information potentially help guide prostate cancer treatment, but it also makes both him and his clinician aware of the potential for additional cancers.

The results of the Philadelphia Prostate Cancer Consensus Conference can be read in detail in the *Journal of Clinical Oncology* 36, no. 4 (February 2018), 414-424. Their considerations included the following:

- which men should undergo genetic testing for prostate cancer;
- which genes should be tested based upon clinical or family scenarios;
- how the testing results should be used to inform screening for prostate cancer; and
- how results should be used to inform treatment of early stage (localized), advanced stage (high-risk), and metastatic prostate cancer.

Genetic testing done thoroughly and properly can help guide screening and treatment decisions.

The National Alliance of State Prostate Cancer Coalitions strongly endorses the use of genetic testing and genetic counseling for prostate cancer, and urges clinicians to read, consider, and follow the scientifically sound suggestions of the 2017 Philadelphia Prostate Cancer Consensus Statement on the Role of Inherited Prostate Cancer Risk. NASPCC will be presenting a Webinar on Genetic Testing and Genetic Counseling in Prostate Cancer on May 9, 2018. It is supported by Myriad Genetics. (Visit https://naspcc.org/index.php/may-9-2018-naspcc-webinar to register.) Pp

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