Prostatepedia[1]

[1]expert insight + advice

Genomics Clinical Trials

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In this issue....

This issue is devoted to the genetics and genomics of prostate cancer, which is one of the most promising and exciting areas of prostate cancer research. Already, this line of investigation is having a major impact. For example, by better defining the genomics of patients entering clinical trials, there can be a marked reduction in the number of patients needed to reach statistical significance. This can potentially reduce the costs of drug development dramatically.

Research into the role of genetics and genomic alterations in the biology and treatment of prostate cancer are still at a much earlier stage than it is for breast cancer. While laboratory studies have discovered a wide range of genes that might act to determine prostate cancer behavior in the clinic, proof that these changes actually determine outcome in the clinic are rather limited. There are even fewer examples where drugs attacking these changes have been FDA-approved for the treatment of prostate cancer.

The PD-1 inhibitor, Keytruda (pembrolizumab) is at present the only example. In 2017, this drug was approved to treat cancers that show mismatch repair or microsatellite instability. These mutations are found in a small proportion of prostate cancer patients.

There are a number of mutations targeted by drugs that are in advanced testing, so this list may expand rapidly. One of the more promising targets is BRCA2. Mutations that alter the function of this gene are known to be involved in breast and ovarian cancer. Cancer cells with these BRCA2 mutations become dependent on the protein, PARP, for their survival and drugs that inhibit PARP can be effective therapy. Studies on patients with advanced prostate cancer show that altered BRCA2 is found in 10-30% of cases. PARP inhibitors have shown significant activity in early clinical trials. Randomized controlled trials needed for FDA-approval are in progress.

Genomic information can also be used to determine how likely prostate cancer is to behave aggressively. This can help identify patients who are likely to do well with active surveillance or to be at low risk for recurrence after an initial attempt at curative treatment.

While genomics promises to revolutionize the treatment of prostate cancer, this revolution requires support from the patient community. The key studies can only be done if patients elect to participate in these trials. For this reason, we made sure to provide you with information on how to become involved in this process.

Charles E. Myers, Jr., MD Pp1

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Prostate Cancer Genomics

Dr. Leonard Gomella is the Bernard W. Godwin, Jr. Professor of Prostate Cancer and Chairman the Department of Urology at the Sidney Kimmel Medical College in Philadelphia, PA.

He is keenly interested in developing of new diagnostic techniques and treatments for prostate, bladder and kidney cancer and has authored over 300 papers, chapters and monographs in urology.

He spoke with *Prostatepedia* about prostate cancer genetics and genomics.

Why did you become a doctor?

Dr. Leonard Gomella: I was a lost high school student. I went to a very good Catholic high school where I was encouraged to think about what I wanted to do with my future beyond college. As I became more interested in science, it became apparent that a lot of the practical applications of science had to do with healthcare and medicine. I had also worked on an ambulance and that impressed me. There's a lot you can do for people and very significant impacts you can make on an individual's and a family's life if you're in healthcare. Nobody else in my family had ever gone into medicine, so it wasn't like my father or grandfather influenced me. It was just something that evolved. Again, I trace it back to my high school days when the Marist Brothers encouraged us to think way beyond high school and college, down our whole life pathway. I'm very grateful to them for leading me in this direction.

That's interesting. It's unusual for a high school to be that forward-thinking.

Dr. Gomella: It was a very unusual high school environment. My experience was different than that of a lot of the kids in my neighborhood who went to other schools.

Have you had any patients over the years whose cases changed either how you view the art of medicine or how you view your approach to treating patients?

Dr. Gomella: I do mostly urologic cancer, and fortunately, most of my patients tend to do well. We have a lot that we can do to give them a good quality of life, and in many cases, actually cure them.

In the face of basically death, the strength of the majority of patients to just continue on with their lives even though their prognosis was poor has always impressed me the most. That is amazing to me. If I were facing that, I don't know that I could be as positive. I admire these patients for being able to deal with these situations.

Yes, men face the potentiality of death. You never know how are you going to react to that.

Dr. Gomella: Right. We're all in the same line—death and taxes, but when the reality is suddenly there, I'm impressed by people's resilience, and how they can handle things. I hope I can handle things as well as most of my patients do.

What is the difference between genetics and genomics?

Dr. Gomella: Genetics and genomics used to be very distinct, and today they've become blurred together. Traditionally, genetics is what you inherit from your mother, your father, and your grandparents whereas genomics is a fairly new term that refers to all of the information contained within a single cell in your body in your DNA. As we've come to realize that your genetic inheritance is what appears in the genomics of your body, genomics and genetics have merged together. They branch off a little bit because you can trace your genetics through your genomics.

Genomics becomes complicated because it looks at not only the DNA in your cell, but also at how these different DNA components interact with each other and the environment. This interaction can lead to either the cure or cause of disease.

Again, the two are coming together as a single concept, but the details of genomics are becoming incredibly complex for patients in terms of prognosis, designing treatments, and precision medicine. In lectures, we will sometimes use the terms interchangeably.

What do we know about inherited risk of prostate cancer?

Dr. Gomella: In the majority of patients, prostate cancer is sporadic. In other words, we can't trace a specific inherited gene or inherited predisposition to the cancer in the majority. However, we can identify some familial risk factors for prostate cancer in about 10 to 15% of men. Familial risk factor doesn't necessarily mean prostate cancer.

There are a series of cancers that can occur in relatives of the same family, but they're not the same cancer. This means that, when you start to look at family trees and family histories of men with prostate cancer, you may identify other hereditary familial cancers. For example, there could be breast cancer in a grandmother or colon cancer in a sibling. We have identified hereditary cancer syndromes, but we still can't figure out any kind of inherited risk for prostate cancer. In 10 to 15% of cases, we can identify some inherited genetic or genomic alteration that has passed down from generation to generation that increases the risk of cancers.

The genes that everyone hears about, such as the BRCA1 and BRCA2 genes associated with breast and ovarian cancers, the genes that Angelina Jolie famously discussed a few years ago, are only genes that may act as accelerants. In other words, they do not cause breast cancer. They do not cause ovarian cancer. And they do not cause prostate cancer. When these genes are present, they tend to make the cancers act more aggressively. That's an important distinction.

We don't know what causes prostate cancer. We just know that, if patients have these certain genes in their DNA, and if they develop prostate cancer, the prostate cancer tends to act more aggressively.

What kinds of genomic tests are available to patients and what do their results mean?

Dr. Gomella: Many people reading this are familiar with other molecular biology tests, such as Polaris, GPS, and Decipher. It's very important to distinguish those from genetic and genomic testing. Those three tests are done on the prostate tissue itself and give an idea about the cancer's aggressiveness.

The genomics of the cancer itself versus your own genomics, correct?

Dr. Gomella: Absolutely, the genomics. Those tests show what's going on in your cancer itself and not necessarily what you inherited.

When we talk about genetic and genomic tests in prostate cancer, we're testing for the inherited genes that we can sometimes trace through a family to suggest that if a man does develop prostate cancer, it may need to be monitored or treated differently.

The top genes that we tend to talk about in prostate cancer are actually the same genes that we refer to in breast and ovarian cancers, the BRCA1 and BRCA2 genes. If a lady inherits those, she's more likely to develop an aggressive ovarian or breast cancer. And if a man inherits those same genes, he's more likely to develop an aggressive prostate cancer. And the net becomes wider. When patients have more common cancers like breast and prostate cancer along with certain genes, this can increase the risk for a patient to develop other related hereditary cancers. Familial history of cancer syndromes mean increased risk of melanoma, colon, and pancreatic cancers.

Right now, we have about a dozen hot-button genes in prostate cancer, but as we do more and more research, that number will expand. The big genes we talk about for prostate cancer are BRCA1, BRCA2, ATM, and CHEK2. The list is much longer than that, but these are the ones that are most commonly identified in men who have inherited prostate cancer risk.

What does it mean if a man has these?

Dr. Gomella: If we identify that a man has these altered genes, we may do different things for him. For example, we may start screening him for prostate cancer at an earlier age. If he develops prostate cancer, we may recommend surgery or radiation over an approach such as active surveillance.

It could be more aggressive?

Dr. Gomella: These genes are important in advanced prostate cancer. We have developed, and will soon have approved, a series of drugs that are more effective in men who have both widely metastatic prostate cancer and these genetic alterations. The impact right now is built into the spectrum.

If it's at the early end, we may encourage a man to undergo early prostate cancer screening. At the far end, if a man has bad metastatic prostate cancer, and he has these genetic alterations, it may direct us to some new treatments for him.

Would you say a man who doesn't have prostate cancer should get tested for these genes and then screened earlier?

Dr. Gomella: Right now, we have no recommendations that a man should go out and get checked for these genes. These genes get checked because a family member has been affected with prostate, breast, ovarian, melanoma, or pancreatic cancer, and so that patient sits down with a genetic counselor, and they do a family tree. As part of that counseling session for the patient, the counselor may suggest that the patient consider genetic testing. If he's got the gene, then he may want to think differently about screening. He may want to think about being screened a little bit earlier, or maybe change how often his PSA is checked.

Right now, men should not go out and just start getting all this genetic testing. In fact, we're running into a little problem with this direct to consumer breast cancer screening through genetic testing. They're not checking for the thousand different genetic alterations and report back on only a few genes.

In all the genes we're discussing, we're talking about mutations in them that lead to malignancies. When we say BRCA1 or BRCA2, we're talking about genes that are not acting the way they should. These genes when mutated predispose patients to the development of these malignancies.

Actually, there is no single altered BRCA1 or BRCA2 gene. If you go into the government's large genetic testing database, there are over 900 recognized mutations in these genes. You can have many different forms of a mutated gene.

But these commercially promoted genetic tests for things such as breast cancer only check for a couple of genes, and we don't have that for prostate cancer yet. They're not checking for all the genes that might be out there, so we have some frustration when it comes to widespread genetic testing, be it for breast or prostate cancer. Right now, we're not advocating that. Many of us do support following the guidelines of organizations where, if you've got a strong family history, you get screened.

What's a strong family history? You've got two or three close relatives who've had prostate cancer. You've got a couple of close female relatives who've had breast or ovarian cancer or there is pancreatic cancer or colon cancer in the family. That's when it's worth having a discussion with a genetic counselor. But I wouldn't encourage people to just go out and start having genetic testing unless there is some indication from a professional healthcare provider that you may be at risk.

Remember, the majority of prostate cancers are sporadic, and we have not yet identified a genetic component. However, if you develop prostate cancer, and if you've got that genetic component, we really want to know who you are.

You hear a lot about genomics and genetics in the mainstream news, but you don't hear a lot about genetic counseling. Has that profession kept pace with the explosion of services that are available to the average consumer?

Dr. Gomella: We have a dramatic and growing shortage of genetic counselors in this country. Thomas Jefferson University has a Master's level program for genetic counselors. This is a tremendous growth area. If somebody's interested in healthcare, but doesn't necessarily want to get involved in the blood and guts of being a surgeon or an anesthesiologist, this is a wonderful way to become involved in healthcare.

Of the seven or eight legitimate genetic testing companies (ones that are not just out there asking about ancestry), most offer patients the opportunity for a quick initial telephone consultation with a genetic counselor to review their genetic test. We're grateful for that.

When it really gets down to the details, you want to sit down with somebody and map out a family history. You should go to a genetic counselor at an NCI-designated cancer center or a community cancer center, places where they may have access to these individuals. There's a real need for them.

Do these large companies offer genomic counseling for people before they take the test—before they become customers—or is it only after you've taken the test?

Dr. Gomella: It wouldn't be within their purview to give you medical advice before you get the test. That's up to you and your doctor, your nurse practitioner, or whoever you're working with. Again, I might stand corrected on this, but to my knowledge, their role is after you've had the genetic testing and something has shown up that they give you the opportunity for a one-time telephone consultation with one of their counselors.

If someone reading this thinks they should talk to a genetic counselor, how do you suggest they go about that?

Dr. Gomella: All healthcare is local, so start with your local provider, be it your urologist, radiation oncologist, or medical oncologist, and get their advice. They'll know. They'll be hooked in at some level with genetic counseling. That's what I would say: talk to your provider.

Some of our colleagues, medical oncologists, urologists, and radiation oncologists actually feel comfortable with doing a preliminary screen of the patient. They may even say to a patient that, because no one in the family has prostate, breast, or ovarian cancer, the patient probably doesn't need to have genetic testing. There are colleagues in medicine who feel comfortable with that level of decision.

I happen to be adamant about interaction with genetic counselors because I work with researchers and great physicians who have specific training in genetic counseling with a whole team of genetic counselors, so I feel inadequate around them. I'd rather have them do it. I recognize that some communities out there don't have those resources, and they might want to rely on the guidance of their primary providers.

There are quite a few people who are in either rural communities in the United States or in countries that may not have access to this level of genetic counseling. For those people, is there another resource where they can get a listing of available genetic counselors?

Dr. Gomella: Yes, there are websites out there such as the National Society of Genetic Counselors (https://www.nsgc.org/).

As I understand it, genomics is having quite an impact on how we design clinical trials and the direction of research. Can you speak a bit about that?

Dr. Gomella: Genomics is taking over a large swath of medicine, including cancers that we deal with in urology, like kidney, bladder, and prostate cancers. Remember how we used to test if spaghetti was done by throwing it against the wall to see if it would stick? That's the way we used to do clinical trials. We would take a whole bunch of patients, treat them with a drug, and determine if it worked. Today, we're much more precise in who we test. This is the whole concept of precision medicine.

A lot of clinical trials right now are designed based on the specific genomic profile of a patient and their tumor, so that we're not wasting time. You're not taking a hundred patients and treating them with a drug. You have a signal, either from a basic benchtop laboratory study or from an early Phase I clinical trial, that tells you that maybe people with this BRCA1/2 mutated gene are going to respond better. So, you do a trial specifically for those individuals. It's having a major impact on how we define who are the best individuals to respond upfront.

On the other end of the spectrum, we are still doing trials where we take all-comers, but we're now doing biobanking. We keep tumor, blood, and serum specimens. That way, if a promising new biomarker (such as a genomic test) is identified, we can go back in time and determine which patients responded well. Is there something in common with all of them?

This is what we're doing in the clinical trials today: trying to be as precise as possible, to identify the best patient who is likely to have the best response to our treatments.

What kind of impacts does this have on researchers' ability to recruit enough patients? Historically, it's difficult to get trials fully accrued, but now you're being more and more precise. Does that make it even more difficult?

Dr. Gomella: It's actually the opposite. We're now able to limit our patients so that, instead of needing 2,500 patients in a trial to get a result, we might only need 100 to 200 patients. So, it makes it easier for us to accrue. You can do a smaller, focused trial with fewer patients if you can more definitively identify who may or may not respond upfront.

If you look across the board in oncology, there are a lot of fast-track clinical trials that are not accruing 2,000 or 3,000 patients like they used to, but they're being approved based on a 300- or 400-patient trial.

Which is probably more cost effective in the long run, isn't it?

Dr. Gomella: Absolutely. We're being very focused and more efficient.

Is there anything else you think men with prostate cancer should know about genetic and genomic testing?

Dr. Gomella: This is a rapidly evolving field, and not all men need to undergo genetic or genomic testing for prostate cancer at this point in time. If there's a strong family history of prostate or the other hereditary related cancers that we talked about, then you may want to think about engaging a genetic counselor to see if it's worthwhile getting tested.

While not every man needs genetic or genomic counseling, would you say that every man should probably have at least a brief conversation with a genomic counselor?

Dr. Gomella: At this point, I don't really think so. There has to be a signal. There has to be some reason that you're doing it. Over 80% of prostate cancers are sporadic. There's no family history that you can trace.

Most are not aggressive anyway, correct?

Dr. Gomella: That's correct. We want to identify guys who have the aggressive, life-threatening cancers that really need to be treated. Pp[1]

Felix Feng, MD
Frontiers in Prostate Cancer Genomics

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 the state of genomics for prostate cancer today.

What would you like prostate cancer patients to know about the state of genomics for prostate cancer today?

Dr. Feng: Genomics is becoming an important reality for patients with prostate cancer. We've talked about genomics for years in the context of research and possible advances for patients, but we are now reaching the era when these advances are being used in clinical practice or being assessed in clinical trials.

For patients with metastatic prostate cancer, patients with alterations and mismatch repair genes should be treated with immunotherapy (checkpoint blockade) at some point in the course of their treatment. At some point in their treatment, patients who have alterations in the BRCA1 and BRCA2 genes or other DNA repair genes should also enroll on a trial involving a PARP inhibitor.

There are many other trials testing specific biomarkers for selection for patients. For example, a few years ago, Prof. Johann de Bono presented the results of a study looking at an AKT inhibitor for patients with PTEN deleted prostate cancers. That's currently being explored in a Phase III trial, and we're eagerly awaiting the results of that.

In addition, the presence of androgen receptor (AR) splice variants is being used to select patients for studies. These need to be tested out. Some are molecular biomarkers rather than genomic biomarkers. But for patients with metastatic prostate cancer, we can point to definite examples where science is becoming clinical reality.

In the context of patients with localized prostate cancer or non-metastatic prostate cancer, we're also seeing a number of advances. There are several tissue-based biomarkers that are now covered in various contexts by insurance companies, and they can be ordered as standard-of-care clinically.

In one of my roles, I chair the Genitourinary Cancer Committee for the Clinical Trials group NRG Oncology. A number of our national trials are Phase II and now also Phase III. The trials that we're developing incorporate these genomic biomarkers for patient stratification or patient selection. When you start to see genomic markers like Decipher incorporated into NRG or PAM50 trials, it means that, sooner or later, these will become standard-of-care, assuming that the trials are positive.

Are there any open and enrolling clinical trials that either focus on prostate cancer genomics or incorporate genomics into their design that you think men reading this may either want to look into or ask their doctors about?

Dr. Feng: Two of the most promising studies are in patients who have had surgery for prostate cancer and now have a PSA recurrence. They are both actively enrolling.

"For patients with metastatic disease, there are a number of PARP inhibitor studies in development right now."

The first trial that I would highlight is NRG-GU006. This study is open at hundreds of hospitals in the United States and Canada; it takes men who have a PSA recurrence after prostatectomy. We go back, we profile the prostate cancer sample from those patients, and we assess a biomarker called the PAM50 classifier, which we helped validate in prostate cancer as predicting response to hormonal therapy. Patients get stratified by this biomarker and are then randomized to standard-of-care, which is radiation alone, or to radiation plus the next-generation antiandrogen Erleada (apalutamide). They get both genomic testing with the PAM50 classifier and randomization, as well as the opportunity to be on Erleada (apalutamide).

Another trial that is actively enrolling is the NRG-GU002 trial, which takes patients who have very aggressive recurrences of their prostate cancer after surgery, and tests them using the genomic classifier Decipher. In the control arm, those with aggressive disease get randomized to radiation and hormone therapy or radiation and hormone therapy plus chemotherapy with Taxotere (docetaxel).

We and other groups have many other trials in development trying to incorporate these biomarkers, but those are the two trials that are open and accruing.

Who are the lead investigators on these two trials?

Dr. Feng: On NRG-GU006, the co-leads are Dr. Daniel Spratt from the University of Michigan and me. On the NRG-GU002 trial, the lead is Dr. Mark Hurwitz from Thomas Jefferson University.

Is there anything else that patients might want to consider?

Dr. Feng: For patients with metastatic disease, there are a number of PARP inhibitor studies in development right now. We're looking to move PARP inhibitors into earlier and earlier disease spaces in select patients, largely based on the presence of DNA repair alterations.

This study using the Genentech AKT inhibitor is exciting to me. It's a Phase III study for patients with PTEN alterations. Not all prostate cancers are the same, but we have traditionally put prostate cancer into one disease. But the many different cancers that comprise prostate disease could be genomically selected or stratified.

That is the future, right? Smaller and more precise categories?

Dr. Feng: Yes. Pp[1]

For more information …

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Clinical Trial:
Zytiga, Lynparza, + DNA Repair Defects

Dr. Maha Hussain is the Genevieve Teuton Professor of Medicine in the Division of Hematology, Department of Medicine, and the Deputy Director of the Robert H. Lurie Comprehensive Cancer Center of the Northwestern University Feinberg School of Medicine.

Prostatepedia spoke with her about a clinical trial she's running, BRCAAway, that looks at Zytiga (abiraterone) and Lynparza (olaparib) in metastatic castrate-resistant prostate cancer (mCRPC) patients with DNA repair defects. (The trial has a ClinicalTrials.gov Identifier of NCT03012321).

What can you tell us about the trial that you're running looking at Zytoiga (abiraterone) and Lynparza (olaparib)?

Dr. Maha Hussain: In prostate cancer, and specifically in mCRPC, data emerging from multiple resources, including the Stand Up To Cancer initiative from a few years ago, indicate that greater than 20% of mCRPC cancer harbor DNA repair pathway aberrations. These types of defects in the tumor will allow the patient to potentially be a candidate for PARP inhibitors. In this regard, PARP inhibitors have had a track record in ovarian and breast cancer. They're currently undergoing multiple clinical trials, including Phase III clinical trials in patients with advanced disease and in different settings of the disease.

A couple of years ago, we published data from an NCI-funded clinical trial where patients with mCRPC underwent a biopsy of their metastatic cancer. The patients were then stratified by the presence or absence of ETS gene fusion and randomized to Zytiga (abiraterone) and prednisone with or without a PARP inhibitor called veliparib.

As part of that study, we also looked at other tumor genomics when extra tissue was available. We discovered that the patients who had tumors with DNA repair defects seemed to respond much better to treatment with Zytiga (abiraterone) with or without veliparib as opposed to the patients who did not have that. This is not something that anyone knew before. After we had published our data, the Johns Hopkins team published data they had on patients who had undergone germline testing and who had received Zytiga (abiraterone) or Xtandi (enzalutamide). They reported similar observations.

This leads me to the current trial, which we call BRCAAway. BRCAAway is a prospective clinical trial for patients who have developed mCRPC for which they have not yet received any specific treatment. Patient will undergo a biopsy, unless they have previous tissue available from either the primary or metastatic disease, and the tissue will then be evaluated for the presence of specific DNA repair defect alterations. Per the US FDA guidance, patients who have BRCA1, BRCA2, and/or ATM are randomly assigned to either Zytiga (abiraterone) + prednisone, Lynparza (olaparib), or combination Zytiga (abiraterone) + prednisone and Lynparza (olaparib). Any patient whose tumors have other DNA repair defects (not BRCA1, BRCA2, or ATM) are enrolled into an exploratory arm where they will receive Lynparza (olaparib). Lynparza (olaparib) is provided by the study.

The patients who are randomized to the arm of the Zytiga (abiraterone) or Lynparza (olaparib) can cross over to the other treatment if their cancer is progressing; i.e., if a patient who is randomized to Zytiga (abiraterone) and prednisone and then develops progression of the cancer is interested and his physician deems it appropriate, he can switch over to Lynparza (olaparib). The same is the case for patients who are randomized to Lynparza (olaparib) if they progress on frontline Lynparza (olaparib), they can switch to Zytiga (abiraterone) and prednisone per standard-of-care.

Are you assuming that these patients have already been tested for BRCA1, BRCA2, and ATM, or will you be testing for that?

Dr. Hussain: So long as it was done in a certified and appropriate lab, we can accept the data for patients who have been tested. The study covers a biopsy and the genomic testing for the patients.

Are there any fees associated, or is everything covered?

Dr. Hussain: Anything that's standard-of-care is billed to insurance. Anything that is a research procedure, as in the biopsy and the genomics testing, is covered by the study. The Lynparza (olaparib) is provided by the study, but the Zytiga (abiraterone) is not because that's part of standard-of-care.

All of these tests to assess the cancer, assess tolerance, and assess the cancer progression in terms of scans, things like blood work or anything for safety assessment, per CMS rules, are billed to insurance.

How many patients have you already enrolled, and how many are you looking to enroll?

Dr. Hussain: In the arm with the BRCA1, BRCA 2, and ATM, we need 60 patients. We're about halfway there. We have enrolled 40 patients to date. For the exploratory arm, we have expanded our limit, and we're growing that arm. So far, we have plenty of room to accrue more patients.

How many sites do you have?

Dr. Hussain: We currently have 15 active sites.

That's a lot.

Dr. Hussain: It's a lot of sites, but as I'm sure patients appreciate, part of it is that by the time we see an eligible patient, they have to have the specific mutations, whether it's on new tests or based on previous tissue. When we test, it's roughly one in five who will likely be positive. Of course, they have to qualify by other criteria, so we have to screen many patients.

We're on track as we forecasted, and we're hopeful to finish enrollment by a year from now. We also hope to have some important data to share.

Wow! That's fast.

Dr. Hussain: Of course we need adequate follow-up to assess clinical benefit and its duration. I'm thinking 2020 will be the end of the study, and if there are signals earlier, we will be reporting the data.

The Prostate Cancer Clinical Trial Consortium (PCCTC) is acting as the coordinating CRO. The institutional review board (IRB) of record is Northwestern University IRB. If you're interested in learning more, please visit https://clinicaltrials.gov/ct2/show/NCT03012321?term=brcaaway&rank=1 or email cancertrials@northwestern.edu.

Is there anything else you want patients to know about this particular trial or about the context in which it's occurring?

Dr. Hussain: This and other clinical trials are important options for patients to consider. Clearly, they have access to regular standard-of-care treatment. The hope is that we can do better than standard-of-care. We are also trying to validate earlier observations that I mentioned regarding whether the patients who have DNA repair defects have better response to Zytiga (abiraterone) and how does this response compare to Lynparza (olaparib) versus the combination.

Lynparza (olaparib) is a drug that's available on the market for breast and ovarian cancer, so there's a fair amount of experience with it. It is not yet FDA approved for prostate cancer, but we have a reasonable understanding for the potential side effects. Certainly, there are multiple clinical trials that are looking at it and other PARP-inhibitors in prostate cancer.

Zytiga (abiraterone) is standard-of-care and FDA approved. It's been around for many years. All treating oncologists should be very familiar with it and how to monitor and what to expect.

It looks like an exciting trial.

Dr. Hussain: We are very excited. What is clear from the experience with prostate cancer is that *one size does not fit all*, this is one of the first examples of precision medicine in front line mCRPC. Our goal is to better personalize care and significantly impact disease outcomes.

The patient is our partner. We cannot succeed and deliver better treatments to patients without their partnership, so we are very grateful to them for their participation. Pp[1]

Clinical Trial: Free Genetic Testing

Dr. Heather Cheng is an Assistant Professor at the University of Washington and Fred Hutchinson Cancer Research Center, and the Director of the Seattle Cancer Care Alliance Prostate Cancer Genetics Clinic.

Prostatepedia spoke with her about a clinical trial she's running that looks at inherited genetics of men with metastatic prostate cancer.

What attracted you to medicine?

Dr. Heather Cheng: There are a couple of things I love about medicine and especially oncology. One is getting to know patients, finding out what's most important to them as people, and using that information to help guide discussions and decisions about their treatment in a way that is true to what is most important to them. These days I guess you call this shared decision-making. That's the most rewarding part about what I do.

Have you had any patients over the years who have changed how you see your own role or how you view the art of the medicine?

Dr. Cheng: I have a lot of patients who fit those criteria. My interest in this area started when I was a first-year Hematology and Oncology fellow. I was in the clinic and it was when we were at the beginning of this wave of new exciting drugs that prolong survival, such as Zytiga (abiraterone) and Xtandi (enzalutamide).

I met this patient who was 43 years old; he had new, aggressive metastatic prostate cancer. His disease blew through every one of the new drugs. It was extremely humbling and disappointing because we were so excited about these drugs, but they didn't do much to slow his disease. And it was heartbreaking because he was so young. He had a family history of cancer but not prostate cancer. He had a teenaged son. We had a lot of discussions about the effect of his disease on his son. I wondered if there was something genetic, something that was making his cancer so aggressive. And then, what could this mean for his son? His memory has stuck with me.

When I think about the work and research that I do, it's not just for the individual patient in front of me. I'm also thinking about how we can improve things and advance the field so things can be better for the next generation. How can we make progress as quickly and with as much positive impact as possible?

I met another patient who had a great effect on me. He had just been diagnosed with high-risk prostate cancer, Gleason 9. He was planning to get radiation. As part of a research study, we offered to sequence the DNA of his cancer because he had an unusual appearance of his cancer–ductal histology. He was kind and generous enough to volunteer and participate. It wasn't going to affect his treatment, but he agreed to help us learn more.

In his cancer, we found a mutation in the BRCA2 gene, the one that many people may have heard of because of its association with breast and ovarian cancer risk. There was suspicion that the mutation could be inherited, so we brought him back for dedicated genetic testing for inherited cancer risk. And, it turns out he did have an inherited version of that mutated BRCA2 gene. He was the first person in his family to be found to carry the mutated version of BRCA2. Neither he nor his family would have known until later if we had not looked in his tumor.

After this, some of his relatives had genetic counseling and were also tested. The sister who had breast cancer had a recurrence and was found to carry the BRCA2 mutation. This information was important for her because it offers additional treatment opportunities for her cancer that might not have otherwise been considered. His daughter was also found to carry the BRCA2 mutation and after learning of this, had a mammogram and was diagnosed with breast cancer. She's still curable, so she's going through treatment, but it is possible that she might not have known until much later otherwise.

The importance of test results can extend to relatives in a way that might help more than one person, not just the person that I see in the clinic, but other members of their family. I do want to be clear that these mutations are not found in most people—even those with cancer—but for the people who have these mutations, it can be life saving information for their family members.

What will you be doing, and what can men expect to happen, during your clinical trial?

Dr. Cheng: You can learn about the study from your doctor, support group, or by visiting our website, www.GentlemenStudy.org. There is information about the study. You can consent online, confirm that you have metastatic prostate cancer, and check that you're interested in genetic testing for cancer risk.

There is a questionnaire that many take about 40 minutes to complete, that asks about your knowledge of genetics, basic health, family history of cancer, and demographic information about where you live. You can upload supporting information about your diagnosis, or you can check a box saying you'd like help from the research team to gather that information on your behalf. Because there are strict privacy laws around medical records, you need to give permission to our team to get medical information for the study on your behalf.

To be eligible, you must have metastatic prostate cancer and must live in the United States. There's one other exclusion, which is that if you have some blood disorders such as leukemia, we cannot be sure that the test results are valid.

If you meet criteria, you will be mailed a saliva kit, a medical-grade genetic test through Color Genomics, with instructions on how to provide a saliva sample. Follow the instructions carefully and then mail the kit back. Results are typically available within 4 weeks. You will have access to a genetic counselor following your results, and you are invited to follow up in person to our clinic if you live in the area. If you don't live near us, we can direct you to resources to find a genetic counselor for in-person visit or by telehealth.

The testing for this study is not recreational testing. It is not the same as Ancestry.com or 23andMe. This is clinical, medically appropriate testing if you have metastatic prostate cancer.

Do you share this information with their doctor, or is it up to them to share the information with their doctor?

Dr. Cheng: We strongly encourage participants to share the results and information with their doctors, but our ethical board does not allow us to do this for participants without their specific consent.

Are there any fees for patients?

Dr. Cheng: There is no fee for the patient.

It sounds similar to the process for the Metastatic Prostate Cancer Project, except I don't think they share their results.

Dr. Cheng: Yes, it is similar to that project. The difference is that the patient or the participant gets results that apply to them individually. The Metastatic Prostate Cancer Project, which is fantastic and an important and innovative study, is de-identified, and the patient doesn't get individual-level results back.

Their goal is to amass as much data as they can for research.

Dr. Cheng: Correct, yes.

Are you also cataloging the information that you collect?

Dr. Cheng: Yes.

What will you do with the data that you collect?

Dr. Cheng: We'll be looking at demographics, the proportion of people who have mutations (pathogenic variants), information about family history, and validated measures of knowledge, distress measures and satisfaction with testing.

If patients consent to re-contact, they will be contacted at the conclusion of the study. If there are

other follow-up studies, they can opt to learn about those. There will also be an invitation for those who agree to subsequent studies, like treatment studies or PARP-inhibitor studies, for example.

We're still learning about certain genes, such as ATM mutations and CHEK2 mutations. As we learn more, we may want to update participants on what the field has learned. There are still many important questions that the field needs to answer, and patient engagement and participation will make this happen more quickly. There will be opportunities for those downstream studies.

How many patients are you looking for, overall?

Dr. Cheng: The plan was for 2,000. We have sent kits out to over 350. We still have room for participation!

If anyone reading this is interested, who should they contact?

Dr. Cheng: They can visit www.GentlemenStudy.org.

Why are you doing this particular trial now?

Dr. Cheng: We've known for many years that the risk factors for prostate cancer are age, ethnicity (African American men, for example, are at higher risk), and family history of prostate cancer. We've known that there's an inherited component for a long time, but for a variety of reasons, we didn't have conclusive studies to prove that.

In 2016 we at the University of Washington Fred Hutch Cancer Center and an international consortium found that, even if you don't specifically look at family history or age at diagnosis, about ten percent of men with metastatic disease have inherited cancer risk mutations. These mutations are enriched in people who have more aggressive disease.

"The importance of test results can extend to relatives in a way that might help more than one person, not just the person that I see in the clinic, but other members of their family."

We now have exciting treatments and clinical trials that we believe to be very effective in metastatic prostate cancer with some of these mutations. There is a class of drugs called PARP inhibitors that are currently in clinical trials. In addition, there are platinum chemotherapies that we also believe are effective for these same cancers with similar mutations, even though we don't normally use them in prostate cancer. Knowing about inherited cancer risk mutations can directly impact cancer care by expanding the toolbox with additional treatments that we believe to be especially effective.

Another reason is that, if it's inherited, then their siblings, children, and other relatives may also carry the same mutation, which doesn't necessarily mean they will get cancer, but maybe they want to think about their cancer screening a little differently. Maybe there are things that they could do to reduce their risk of developing cancer.

Previously, there wasn't much genetic counseling done at any point in prostate cancer because the treatment implications were unclear until 2016. It was the appearance of PARP inhibitors and platinum in the metastatic cancer setting that has propelled interest and motivated not just patients, but also doctors to find these men because of the impact to their treatment and the impact to their family.

One major problem is that there was already a shortage of genetic counselors, and the wait times were really long, even when trying to meet the capacity of breast cancer patients. Now we have another common type of cancer, and we don't necessarily have enough genetic counseling resources. I live in Seattle, and we're fortunate to have wonderful genetic counselors in the area, but a lot of people in more rural parts of the state have to drive fifty or one hundred miles just to get to one and that doesn't account for the wait time.

Genetic testing can be important information for men with metastatic disease. We think that the potential benefits are so important that we should look at new ways to deliver this type of care. That's how the GENTLEMEN trial was conceived.

Is there any reason why a person needs an in-office visit for a genetic counselor? Isn't there some way to get the testing done and then do it via telemedicine?

Dr. Cheng: You can, yes. Our study is a modified approach to that. There are a number of issues, including insurers, the lag time for meeting demand, and also how these affect patients. Some patients, for example, have more questions and uncertainty, so it helps to meet in person. Although there are federal laws protecting against healthcare and employment discrimination, there are other implications as well, including life insurance. These are reasons why the role of genetic counselors is never going to go away. They're really critical to this discussion.

To most thoughtfully use genetic counseling resources to make sure the people that most need to see them see them, we will need to change our way of thinking and how we deliver this type of testing.

For some patients who do not have many family members or kids, for example, this might not make them that anxious; it's not a big deal. They have metastatic prostate cancer. They want to know their genetics for their treatment. They're not that anxious, but they need treatment urgently, and they want that information sooner rather than later. Those are the patients for whom this study may be good.

If someone is fortunate and can see a genetic counselor, they can still do that, but then there's an issue of insurance copay. Even if insurance covers it, sometimes the out-of-pocket cost is high. This study removes that barrier because there's no cost to the patient.

On a variety of levels, this study attempts to improve access and find out if this is an acceptable way for men with metastatic prostate cancer to get testing in a novel format. It's patient-driven.

It seems like the shortage of genetic counselors will be increasingly problematic.

Dr. Cheng: We really have to think about how we best use their expertise. We need more counselors across medicine, in cardiology and neurology, for example. Just the fact that we have genomic tools that are less expensive, and now there's more that we can do about them, including treatments, prevention, risk—all of these things—it's going to be interesting to see what happens.

What else should patients know about genetic or genomic testing?

Dr. Cheng: It's a very exciting time. The field is learning about this together, and it's important to talk with your doctors about it, to share family history, and ask questions. Sometimes the information you read about can be confusing, so I encourage you to start and continue those dialogues, know your family history, talk to your doctors, talk to a genetic counselor, make sure you have a good understanding and level of comfort before undergoing testing, and stay tuned because we're making a lot of progress as we go.

We're on the cusp of a revolution, I think.

Dr. Cheng: I think so, and it's very exciting. It's important to get correct information. There's a lot of misinformation or potential for misunderstanding, despite best intentions. Make sure you talk with your doctors. Then make sure you're clear and get information.

We're developing more educational materials for patients that are specific to prostate cancers because so much out there about BRCA1 and BRCA2 genes is focused on women. We're just trying to help educate, but we've also got more to learn.

Does 23andMe also offer this testing to the average consumer?

Dr. Cheng: Yes. My worry about 23andMe is that, while they technically have FDA approval for the founder mutations of BRCA1 and 2, it is not an adequate medical test.

People tested through 23andMe may assume that they don't have a mutation if one is not found. But there is great danger of false reassurance because they only test for three mutations: it's not comprehensive testing. And then people might not get the appropriate test that they need. That's what I worry about.

There was an article in the *New York Times* not too long ago that describes this as an important public health message. People should not assume that because nothing was identified that there isn't something there. The lack of result just means that one of the three mutations isn't there. It's not a comprehensive medical test.

(You can read here https://www.nytimes.com/2019/04/16/health/23andme-brca-gene-testing.html and here https://www.nytimes.com/interactive/2019/02/01/opinion/23andme-cancer-dna-test-brca.html the articles Dr. Cheng references.)

That's a great point.

Dr. Cheng: A positive result may tell you something. But a negative result tells you much less than you might think. It's not comprehensive testing. That is really critical to understand. There are thousands of possible mutations, they only test three, so 23andMe should really be considered recreational and not adequate for medical purposes. Pp[1]

Todd Cohen, MD
Prolaris + Genomic Testing

Dr. Todd Cohen is the VP of Medical Affairs/Medical Director at Myriad Genetics.

He spoke with *Prostatepedia* about some of the molecular clinical trials that he and others at Myriad are currently running.

What attracted you to medicine in the first place?

Dr. Todd Cohen: Probably the clichéd answer… I had an affinity for math and science growing up as a child and figured where I could best use that ability for the best use. It was always medicine from the time I was probably ten or 11. My friends wanted to play baseball and things, and I was a good baseball player, but I figured that wasn't going to make it for me. I always wanted to be a doctor, and I was until two months ago, when I stopped being a practicing clinical physician.

Part of it was that my father was in business, and back in the 70s and 80s, he was always traveling for sales, and so he was always gone. I didn't want a life where I was always gone. I equated business with travel and never anticipated things like what we're doing now, the internet, virtual travel, and discussion.

I'm curious about the move from practicing to working in industry. Why and how did you make that shift?

Dr. Cohen: I felt like I'd done what I could do with clinical medicine. I'd been running my practice as a large group of about 40 providers for eight years. I was doing that and maintaining a busy clinical practice, so I saw that it was time to move on from the business side, let somebody younger with more energy take over. And I groomed somebody to do that.

"If we can identify the low-grade disease and be absolutely certain that we don't need to do anything more aggressive to these patients, that's a big step forward."

I wanted to expand from the clinical side where I could be effective to just a few people sitting in front of me to a vast array of people. It was time for that move.

What about different patients you've met over the years? When you were in practice, and through your current role, have you met patients who changed how you view the art of medicine?

Dr. Cohen: Absolutely. What happens in medicine, and especially thinking for people like myself who deal with cancer patients, we never remember the people for whom it turns out like it's supposed to. We always remember the outliers.

Whether it's the guy who had a terminal disease and survived or just the opposite: somebody we expect would do fine and they don't. We remember the ones who don't respond like we would expect because we never want that to happen again. We become a bit more overcautious, or we look for every possible answer before we make any final decisions.

People think we're worried about getting sued, but that's not it. We're just worried about doing the right thing for everybody. I can't remember my daughter's name half the time, but I can remember every patient whose outcome wasn't what I expected.

What is the context of this trial? Why this trial? And why now?

Dr. Cohen: The trial looks at genomic testing, and in this case the Prolaris test, which is a Myriad test that helps risk-stratify patients to tell if they're more aggressive or less aggressive than you would expect. Part of the trial looks at the utility of this, to get patients into the appropriate treatment path.

A lot of prostate cancer is not lethal. It's a low-grade disease, and probably the cliché line is true: treatment can be worse than the disease. We want to identify the patients who are never going to progress, who will die from the disease or have some bad outcome from the disease. But the vast majority of patients won't have that problem. If we can identify the low-grade disease and be absolutely certain that we don't need to do anything more aggressive to these patients, that's a big step forward.

Two patients that look the same on their clinical parameters, who have the same blood test, PSA, and pathology, may act completely different. We've all seen that as practicing physicians. One guy we'd expect to do fine, doesn't, and another guy we expect to not do well, does. There's no rhyme or reason because prostate cancer is a spectrum of diseases. It's not like: you have it, you've got to do something, and this in particular is what you have to do.

This study is to identify men specifically in the VA system because about 14% of all prostate cancer patients are taken care of by the VA system in the United States. On part one, it looks at gathering to see if we can better identify men who are good candidates for active surveillance.

The second part of the study is looking at long-term outcomes. What happens to these men, especially the ones we expect to do well? Do they actually do well? Can we truly identify, using genomic testing, men who won't ever need to be treated, who won't have adverse problems down the line?

"A good portion of patients who come off active surveillance do it just by patient choice."

The first part is the quick and dirty. We've accrued right now 1,800 men into the study, so we've met our mark. We're going through some data analysis right now as to who's on. Then, we'll watch these men to see if they stay on active surveillance, or if they're more likely to stay on knowing that they have a genomic test that says they really don't need to be treated. Also, we want to see how men do when they seem like they can be on active surveillance and don't need to be treated. This test tells if it's more aggressive, and if you probably should be as well. We want to see how these men fare over time.

We also look at the durability of staying on active surveillance. After a while, many men will not want to do active surveillance anymore. They ask us to treat them. A good portion of patients who come off active surveillance do it just by patient choice. It's anxiety or they're just tired of being watched, so they say, you might as well just treat me.

Then we have guys in their evaluation as they're on surveillance who look like they're progressing, not to metastases or something bad, but to a change in their pathology or their PSA starts to increase in a more significant way. Then there's a joint decision between the physician and patient that it's time to treat.

Is the thought that the Prolaris test would give men the extra confidence to stay on active surveillance, if that's the right choice, or prompt them to more aggressive treatment, if the test indicates that it's needed?

Dr. Cohen: Both. That's the idea. It gives the patient who really wants to go on active surveillance a little bit more confidence that it's unlikely that he's going to progress. Also, it gives the doctor a little bit more confidence that he's doing the right thing for the patient. On the flip side, it could indicate that, though we thought someone was a good candidate for active surveillance from what we saw under the microscope, the test tells us that their cancer is more aggressive.

When I talk to patients about this, and I show them the test, I like to use the car analogy. You have two cars in front of you. They look exactly the same, two Corvettes. They're identical in every respect when you look at them. When you lift up the hood, one might have a treadmill with squirrels. It's not going to go very fast. Then you open up the hood of the other car, and it has a 600 hp motor. That car is going to move. Although they look the same, they're not going to move the same. That's what these kinds of tests can tell you. Do you have the squirrels under the hood, or do you have the big engine?

There's so much information out there about prostate cancer, so the more we can simplify and provide an understanding, the better.

There's something about learning new information while you're scared.

Dr. Cohen: Yes. If we go in, and we're just totally scientific, you're going to look at us confused, and you're only going to hear cancer, and that's the end.

So, you have enrolled 1,800 men, you've given them the Prolaris test, and they have made their choice one way or the other, correct?

Dr. Cohen: Yes.

What does the follow up look like, and how long will you be following them?

Dr. Cohen: Well, we're going to follow them for a long time, particularly because we want to see how their outcomes go and how the test predicts the outcomes, long term. The plan is, potentially, ten years of following the patients. I'm sure we're going to lose a lot of them. Some of them may move. They may get lost in the follow-up. They may die from other reasons, hopefully not from prostate cancer while they're doing this.

The follow-up is structured by each individual site. There's no great protocol for how we place someone on active surveillance. Typically, the deal is you'll take the PSA on a regular basis, usually every six months or so. You'll get a confirmatory second biopsy at about a year after the first one.

For the arm of men who have had Prolaris and have been treated already, they'll be followed on a regular basis, usually every six months for—I could do it every six months forever.

Will the follow-up be monitoring the PSA and imaging?

Dr. Cohen: Just PSA, unless the PSA starts going up, and then we'd add imaging. If a person has a PSA of zero or it's negligible and it's not increasing, there's no reason really to pursue imaging.

Eligibility and fees don't really apply since you've already closed. Are there any other trials that that you are running?

Dr. Cohen: Yes, we're running other trials right now. A lot of them are similar to this, and not just in the VA, where we're looking at long-term outcomes in longer studies.

One of the things we also do besides just the Prolaris testing is the genomic test. There's a big understanding now that hereditary genes like BRCA1, BRCA2, and some others have a high impact on prostate cancer as well. If somebody has the BRCA mutations in the family, men aren't usually checked, but there's been a high correlation now with the BRCA genes and prostate cancer. If they have these hereditary mutations, they're much more likely not only to get prostate cancer but to have aggressive prostate cancer. We're running trials on that.

We're doing registries to look at the prevalence of the gene mutations in men and its association with prostate cancer. For example, we're going to sponsor a registry of African-American men. A lot of the studies out there are heavily weighted to non-African-Americans, so we're doing this to see the prevalence and get a better understanding of the disease

in African-American men. We're also looking at other genes to try to get an idea.

If you're a great candidate for active surveillance, but your mother died of breast cancer, your father had prostate cancer, and you have an aunt that had ovarian, you may be at risk. There's a guy who right now may look like he'd be a great candidate for active surveillance, but we know that he's at much higher risk of dying from the disease, so it's probably not a good idea to watch that kind of guy.

We're also looking at men who are already metastatic. We're using that information to better diagnose, and to see what new treatments are out there.

Are you only looking for men who already know they have, for example, BRCA1 or BRCA2, or will you be testing them to see if they have it? If so, is that testing included in the trial or is it an extra fee?

Dr. Cohen: It depends on the trial and whether it's a registry that's just trying to get an idea of the prevalence. A lot of those registries usually are commercially tested or are a reduced-fee test. For trials that look at drugs with pharmaceutical companies and that require a mutation for eligibility, usually study protocols require that they're provided through the trial.

What about location? Do men have to be close enough to you for a visit, or is this testing that can be done remotely at a variety of places?

Dr. Cohen: It's just a blood test, so it can be done remotely. For the trial specifically for African-Americans, there will be multiple sites all over the country.

If someone reading this is interested in participating in any of these trials, can they contact you or is there someone else they should be in touch with?

Dr. Cohen: They can contact me, and I can get them in touch with the appropriate person at Myriad. We have several people who run these things so it's better to put them all through just one person, and then I can direct them to the appropriate place.

Is there anything else that you want to add about the trials or genetic and genomic testing for men with prostate cancer?

Dr. Cohen: In terms of genetic testing or germline testing, we're 20 years behind the breast cancer doctors. It's a big learning curve for urologists, and they are still wrapping their minds around liability. If they test their patients, do they have to worry about their patients' families? There's a lot of education that still needs to be done for the doctors to understand and to incorporate genomics into their practice. It's something we've never been trained in whereas the breast surgeons and oncologists have been dealing with genomics and germline testing for decades now.

As the media spreads the word, and as patients understand that this is a big part of the future of prostate cancer specifically, that will help. Pp

For more information …

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