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Using Genomics To Guide Treatment

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In this issue....

This month, we're talking about our understanding of the genetic and molecular mechanisms driving prostate cancer. If we can understand how cancer differs from your body's normal tissues, we can selectively kill cancer while minimizing damage to normal tissue. As it turns out, this type of research is very difficult.

How can genetic changes cause cancer? How do they determine the biology of the resulting cancer?

Genetic information is stored in DNA. The DNA molecule is like a library filled with instructions for a cell to accomplish various tasks. At any one point, only a small set of the instructions are activated and followed.

In normal biology, the instructions activated are appropriate to the task at hand: liver cells activate instructions for liver structure and function; muscle cells activate instructions for muscle structure and function.

Normally, these cells' growth and spread are tightly controlled. If you remove half a liver, the liver regrows to its normal size and then stops.

Cancers cells' growth and spread are no longer controlled. Liver cancer cells grow and spread beyond the liver and, if untreated, kill the patient.

How does your body read those DNA instructions?

Your body first creates a RNA molecule that is a copy of the instruction. You use this RNA molecule to produce a protein that makes cells change their structure or behavior.

Cancer behavior comes from a set of proteins that promotes inappropriate growth and spread. Several mechanisms cause the production of these protein sets.

The DNA instruction set itself can change, or mutate. We can detect these mutations in DNA instruction sets through DNA sequencing.

DNA sequencing technology has advanced rapidly and costs less then $1,000/sample. If you can get a sufficiently large biopsy of your cancer, we can sequence the DNA. Foundation Medicine is the largest commercial firm offering this service today.

Unfortunately, mechanisms not involved in DNA mutation, and therefore not detectable by DNA sequencing, can change that RNA copy.

Adding the methyl group to DNA commonly alters RNA copy production and plays an important role in prostate cancer. One approach measures RNA copy production of genes important to prostate cancer biology. Tests like Prolaris and Decipher used in early, organ-confined prostate cancer use this approach.

Another approach measures proteins that control prostate cancer behavior or response to treatment. Caris Life Sciences measures the presence or absence of proteins that determine responsiveness to two major prostate cancer chemotherapy drugs called Taxotere (docetaxel) and Paraplatin (carboplatin).

All of these tests require a biopsy. It is often difficult to biopsy prostate cancer and especially bone metastases. In advanced prostate cancer, we find cancer DNA in the blood. We can isolate and sequence these cancer DNA fragments to identify mutations in a liquid biopsy.

Guardant Health is the most established company in this area. At my clinic, we've used the Guardant360 liquid biopsy extensively to identify hormone-resistance mutations, as well as DNA repair mutations that predict for PARP inhibitor response.

We are only beginning to apply molecular biology to prostate cancer treatment, but the approach has great promise.

Charles E. Myers, Jr., MD Pp1

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James Doroshow, MD
Precision Oncology

Dr. James Doroshow, Director of the Division of Cancer Treatment and Diagnosis at the National Cancer Institute (NCI), spoke with *Prostatepedia* about the promise of precision oncology.

Why did you choose to become an oncologist?

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Dr. James Doroshow: The simple and truthful answer is that I had a remarkable attending physician when I was a medical student at the Beth Israel Deaconess Medical Center in Boston. He was probably one of the best internists, and certainly one of the best medical oncologists, in Boston. He was great with his patients, extremely knowledgeable, and involved in clinical research. I had the opportunity to work as an elective Fourth Year in his office and then to work with his patients when I was a House Officer at Massachusetts General Hospital. He was my role model.

What is precision medicine?

Dr. Doroshow: In the broadest sense, precision medicine aims to choose prevention or treatment therapies for patients based on specific pharmacogenomic characteristics of the patient himself or herself or of their tumor or other disease entity.

"There is a major NCI effort to develop cloud systems to make available to the entire scientific community as much data as we can"

(It might well be that one could develop a precision medical approach to cardiology based on the molecular characteristics of aortic stenosis and the changes in cardiac tissue related to increased pressure of the muscles.) Approaches that one never considered feasible 30 years ago are now becoming feasible.

It's easier to understand how that works in oncology: you're trying to characterize why or how particular tumors grow and then choose either prevention or treatment approaches to that particular oncology problem based on those molecular characteristics.

What is pharmacogenomics?

Dr. Doroshow: Pharmacogenetics uses an individual patient or patient group's germline genomics—the characteristics of their non-diseased tissue—to choose a particular drug or dosage of a particular drug. We understand how the genetic characteristics of normal tissue impact the effectiveness of the treatment or the metabolism of the drug based on the intrinsic molecular makeup of an individual's kidneys, liver, organ, or heart to optimize therapy.

For the most part, pharmacogenomics is used to think about how drugs are metabolized and the genes that affect drug metabolism.

The right dose of the right drug for the right patient?

Dr. Doroshow: There are many circumstances in which pharmacogenomics has made a significant contribution to our understanding of how to better give drugs to patients with non-oncologic disease. There are actually only very few circumstances in which pharmacogenomics has played any significant role to date in how to best dose cancer drugs. There are a couple of drugs for which tests are available, but clinicians don't even use these tests because they don't have to. There are other ways to deal with those problems. It's very different.

You can say the same thing for precision oncology. From an oncologic perspective, it's about the molecular characteristics of the tumor. From a pharmacogenomic perspective, it's about the molecular genetic characteristics of the patient's host tissues.

Pharmacogenomic dosing of drugs in oncology has not had much of an impact so far. That is very different from molecular characterization of tumors for sensitivity resistance, etc.

Is pharmacogenomics being used to predict which patients will respond to which drugs?

Dr. Doroshow: Generally not. In the medical community, pharmacogenomics is used, for the most part, to define in advance optimal dosage to make sure patients are not over-dosed or under-dosed based on their drug metabolism.

What are precision medicine's implications for global and national healthcare costs?

Dr. Doroshow: One can resort to the old saying that nothing ever costs less. That isn't exactly true, but it is often true. If you develop a great new test for something, often it becomes supplementary and added on to the range of studies that doctors order for patients. Occasionally, tests become totally obsolete. Then there is actual savings.

I think molecular diagnostics will not be the cost-inducing portion of the precision medicine perspective. That is to say, we can do a genome for $1,000. Pretty soon we'll be able do a whole genome for $1,000. That costs less than a set of blood work.

For perspective: it costs $1,000 for the genome, $50,000 for the interpretation, and $500,000 for the drug. The test is cheap, but unless you have an automated way of allowing physicians to know how to use it—which nobody has—then you need people to interpret, which is

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expensive. The cost of the test goes down. The cost of the people to interpret the test does not go down.

If you do get an appropriate interpretation of the test, what do we do about the cost of the drugs, which is now so very high? It's not the testing. It's not the molecular characterization that is the issue. It's what comes next after you get those data that is the issue.

What implications do precision oncology and pharmacogenomics have for clinical trial design?

Dr. Doroshow: The very long-term view is that if we get good enough over the next 10 to 20 years at understanding which molecular characteristics actually define who is going to respond and who isn't, then even if it is an absurd amount of money to cure someone, that will probably be a cost savings. Those patients are not then going to develop a hepatocellular carcinoma or cirrhosis and have a lifetime of enormous medical costs that would be far more costly than the price of the drugs to cure.

It really depends on how effective the treatments become and how well we'll be able to choose who to treat and who not to treat.

Are we now looking at smaller and smaller subsets of patients?

Dr. Doroshow: That is clear. There is just no question about that.

Wouldn't that then make you more efficient in your clinical trial design?

Dr. Doroshow: It might if you can isolate those groups and prove that something actually works or doesn't work, but not if we don't already have a treatment for that particular molecular subset.

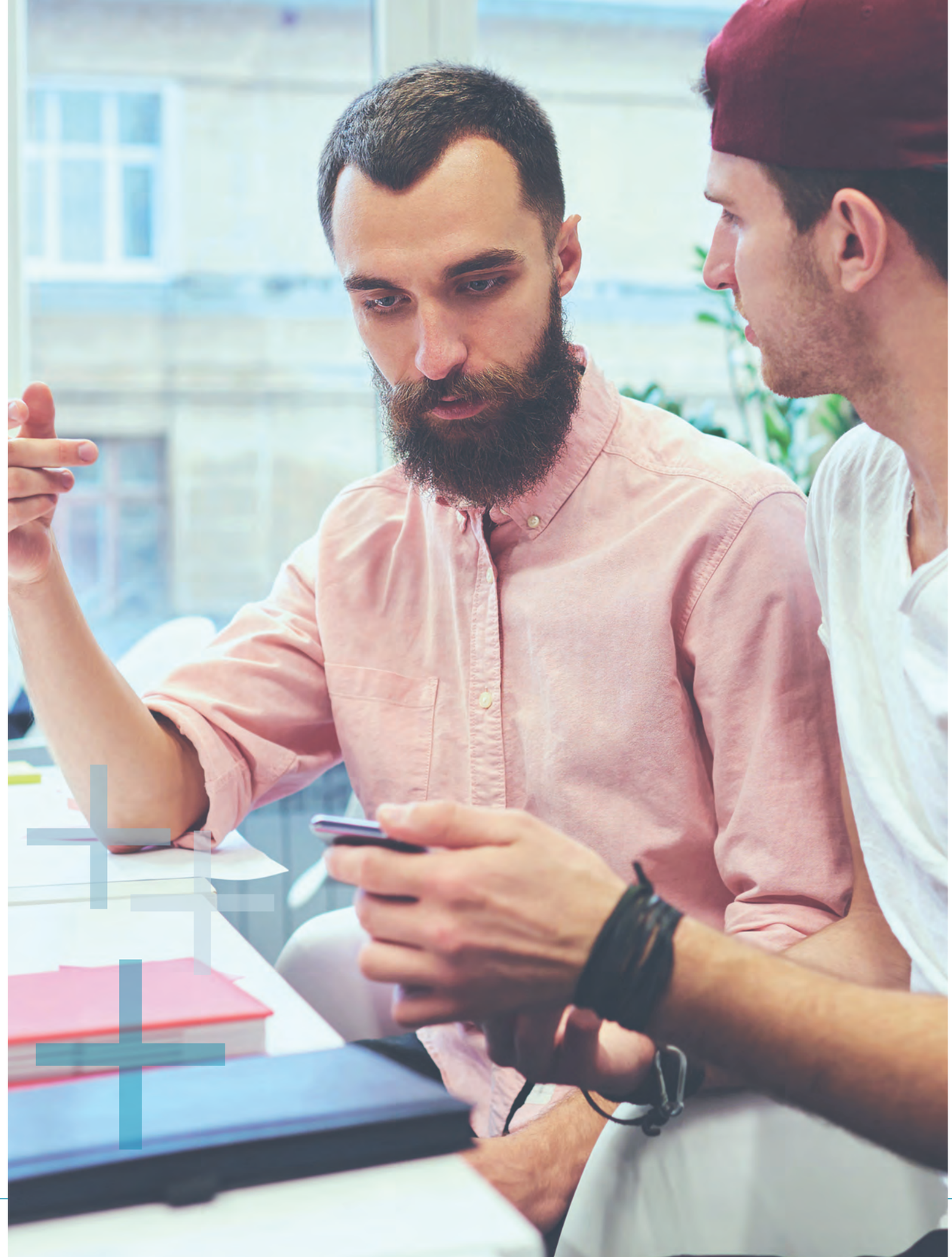
It's fantastic to find out that 50% of patients with melanoma have mutations in the BRAF gene and that those patients respond to a particular drug. But the same drug is completely ineffective for those with the same exact mutation in colon cancer. We have a molecular characteristic, but what is the context? Is it actually going to predict which therapy will be useful?

How are scientists and clinicians managing the massive amount of molecular and genomic data generated during the past few years? Are clinicians able to mine this data to deliver customized oncologic care or is that still an evolving story?

Dr. Doroshow: The first issue is: where is the data, who has access to the data, and how to make the data available? There is a major NCI effort to develop cloud systems to make available to the entire scientific community as much data as we can. There has been an enormous effort over the last decade to develop the systems and to design algorithms to make it useful.

I have no idea whether it's going to take 10 or 20 years to develop ways to analyze this information in a way that makes it clinically useful. That's the trick.

My joke is that in a future in which I will not be practicing medicine, a physician will walk into an exam room and go to his or her computer to see the characteristics of say a breast cancer tumor; the algorithm of the day will predict which will be useful therapies or even rank them in order of usefulness. The doctor will then decide if he or she agrees with the algorithm and push a button; the doctor's job will be to tell the patient what the therapy encompasses and what the side effects will be. By the time the doctor is done with the



30- or 60-minute conversation with the patient, a drone will have the medication ready.

What is extraordinary for me is to remember what it was like when I started. We had absolutely no way to predict whether something was going to be useful or not. I remember drawing blood and running from building 10 to building 37 at the National Institutes of Health (NIH) to give specimens to this lab or that lab. You have to be optimistic.

Which initiatives between health care and tech industries that aim to deal with the massive amounts of information being generated do you think are the most promising?

Dr. Doroshow: There are a bunch of different academic centers and companies all trying different approaches, but it's not yet clear which is the right approach. Over five years or so it will sort out. Google and IBM are in this sphere.

Again, I'm not talking about which algorithm to use, but the approach of amalgamating data in one place so that the data can be queried.

The NIH has an initiative to bank data, but are there other US-based initiatives?

Dr. Doroshow: There are 10 to 15 NCI-designated cancer centers. They have their own corporate entity trying to put together their data.

As I said, there are a bunch of companies—not just IBM and Google, but also startup companies and other bigger companies funded by health care concerns involved. Pp1

William Douglas Figg, Pharm.D
Pharmacogenomics

Dr. William Douglas Figg is the Deputy Chief of the Genitourinary Malignancies Branch and Head of the Molecular Pharmacology Section and Head of the Clinical Pharmacology Program at the National Cancer Institute (NCI).

Dr. Figg applies pharmacological principles to anti-cancer drug and biomarker development. A large part of his research focuses on the development of novel therapies for prostate cancer.

Prostatepedia spoke with him recently about pharmacogenomics for prostate cancer.

How did you come to focus on prostate cancer?

Dr. Figg: I finished my Fellowship in drug development at the University of North Carolina at Chapel Hill in 1992 and went to work for Dr. Charles "Snuffy" Myers in the Clinical Pharmacology Branch of the NCI. Dr. Myers was one of the leaders in prostate cancer at the time. I quickly developed a research interest in metastatic prostate cancer and in developing new agents to treat the disease. As a trained pharmacologist, I approached the discovery and development of new anti-cancer agents via a logical flowchart of *Go/No-Go* decisions.

"This is pretty limited for prostate cancer."

What is pharmacogenomics?

Dr. Figg: Many physicians don't fully understand pharmacogenomics. If you're talking to a clinical pharmacologist, pharmacogenomics are variances in genes that handle drugs. Metabolism enzymes and transporters have genetic variances. These variances may mean you need to change the drug dosages, because your body can't get rid of the drug quickly enough or the drug doesn't transport well into the cell.

On the other side, there are somatic mutations associated with a tumor. Somatic mutations are genetic variances inside of a patient's tumor cell that are different from the patient's normal DNA. We are now able to target those somatic mutations with drugs that may work in that particular tumor.

Is pharmacogenomics used to guide treatment?

Dr. Figg: On the clinical pharmacology side, there are 150 drugs that include pharmacogenetics-related information in the approved label. However, about 30% state a requirement or recommendation for genetic biomarker testing. That is not a lot. Many patients haven't had these tests. (See http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm for a list of these drugs.)

Some of these are anti-cancer drugs, but most are drugs for other indications that have pharmacogenomic testing in their package insert. It is becoming more widely recognized that we have to do germline DNA testing in order to specify the right dose that works and is safe for an individual.

With regards to tumors, we have several drugs for which we look at biomarker or genomic indicators of variances in order to specify if you can or shouldn't take a drug. This is pretty limited for prostate cancer. We've done a lot of testing, but the vast majority of our drugs for prostate cancer don't have a biomarker indicator yet. For other tumors, the biomarkers HER2, BCR-ABL, BRAF, EGFR, PD1, RET, ER, PR and MGMT have been validated.

What are the barriers to patients receiving pharmacogenomics testing before taking these drugs?

Dr. Figg: Some of it is cost. Some of it is been lack of appreciation

that pharmacogenomics testing is important. Some physicians say, "I've given this drug for years without a problem."

For example, Coumadin (warfarin) has been around for decades. Doctors tend to adjust Coumadin (warfarin) dosages based on bleeding time. We now have genetic markers that can make that first dose specific, so you don't have to do trial-and-error dosing—increasing and decreasing dosage until you get it right.

My vision for pharmacogenomics is that eventually we will genotype a child at birth; that information would then go into an electronic medical record (EMRs). Then, every time a physician needs to prescribe something, he or she will already know if that individual can safely take the drug or not.

Inova Fairfax Hospital in Virginia offers pharmacogenomics testing to all infants born at their hospital (approximately 10,000/year); about 80% of parents consent to the test. Those children will now always have that information in their electronic medical records.

Would that reflect a cost-saving? If you could get the right dose for a patient…

Dr. Figg: That's the selling point. For around $500 you can get a panel of about 200 genes that encompasses all of the drug metabolism and transport genes for an individual. Insurance companies are now realizing that it is probably in their interest to do this: it is much better if you can prevent someone from having a bleed or prevent a hospitalization or get more efficacy from a drug.

There was a case report in the *New England Journal of Medicine* in 2009 about a toddler who had an adenotonsillectomy. Doctors gave him Tylenol 3 (acetaminophen plus codeine) after surgery. Codeine is metabolized to morphine via CYP2D6. It turns out this child was an ultra rapid metabolizer of codeine. He died from morphine toxicity. This case struck home with a lot of healthcare providers: we should be doing pharmacogenomics testing more often.

Camptosar (irinotecan), a colon cancer drug, offers another example. Diarrhea is one of the main limiting factors associated with the drug. We can now genotype the enzyme UGT to predict who will not tolerate Camptosar (irinotecan) because of diarrhea.

Another example: Mercaptopurine (6MP) is used to treat childhood leukemia and is metabolized by the enzyme thiopurine S-methyltransferase (TPMT), which is polymorphic. That means a small percentage of individuals cannot metabolize through TPMT (0.01% to 1%) and 2% to 20% are intermediate metabolizers. For those deficient in TPMT, you need to give them 10% to 15% of the original dose and give approximately 65% of the normal dose to intermediate metabolizers. Everyone else can tolerate the full dose of that drug quite well. If you happen to give a full dose to a child with a variant for the enzyme TPMT, you could cause serious harm and possible death.

Are there any implications for prostate cancer patients? Many men with prostate cancer are on a variety of medications for conditions not related to prostate cancer.

Dr. Figg: Yes. One, your doctor has to look at drug interactions. There are drugs that inhibit or increase metabolism of anti-prostate cancer drugs.

My lab at the NCI is at the forefront of trying to understand the variances that predict who responds to chemotherapies such as Taxotere (docetaxel). We are very interested in transporters that may move androgens into the cell. We know that these transporters become up-regulated in advanced prostate cancer.

"Insurance companies are now realizing that it is probably in their interest to do this"

We have identified one variant in that genome that could predict your response to androgen deprivation therapy. We're not at the point of having any kind of guideline for saying you should be doing this type of testing, though. This is still in the research phase. But we're working towards the end-goal of being able to say, "Let's genotype you as soon as you're diagnosed with prostate cancer. We'll then adjust your therapy based upon that information."

What would you say to a reader who'd like to get tested now?

Dr. Figg: I recommend readers talk to their doctors. Depending upon the drug therapy they're currently on, it may not be necessary right now. If your doctor prescribes something in the future, then it may be worth it. But talk to your doctors. They can order the test.

Again, it's a small list and the drugs aren't common, but a lot of prostate cancer patients are on Coumadin (warfarin). If you're already on a standard dose and you're regulated, then it's perfectly fine. You don't need to know your genotyping.

But if you're just starting on Coumadin (warfarin), it can really help find the right dose for you.

What are some of the barriers to global adoption of genomics to guide treatment? (That is a pretty ambitious goal: to have everybody genotyped at birth.)

Dr. Figg: We need a full appreciation of the potential side effects of drugs and how we can limit those side effects with genotyping. That appreciation has to come from the medical community. Once they fully understand that they can guide therapy more specifically, or pick the right dose or right drug for an individual, they will be more inclined to do this for their patients.

What implications do genomics and pharmacogenomics have for rising health care costs?

Dr. Figg: For pharmacogenomics to impact health care costs, we need studies that show we've prevented hospitalization by genotyping. We need studies that show we've prevented serious complications associated with drugs. And studies that show we had to put fewer patients on a clinical trial in order to get the activity level we're seeking.

On the other hand, we can select patients who will have the best response to therapy by genotyping. Instead of doing a 1,000-patient study, we may only have to do a 300-patient study to show that a specific drug is more effective than standard of care. We're trying to select the population that will have the best response to treatment. This can reduce clinical trial costs and make it faster for drugs to gain FDA-approval. Pp

Dr. Joshi Alumkal, MD
Genomics

Dr. Joshi Alumkal is a medical oncologist and Co-Leader of the Prostate Cancer Research Program at the Knight Cancer Institute at Oregon Health & Science University (OHSU) in Portland, Oregon. His lab at OHSU focuses on identifying ways by which prostate cancer evolves into the lethal form of the disease.

Prostatepedia spoke with him recently about how doctors hope to use genomics to guide treatment.

How did you come to focus on prostate cancer?

Dr. Joshi Alumkal: I became interested in prostate cancer research during my Fellowship at Johns Hopkins Hospital in 2002. Prostate cancer treatment and research were one of Johns Hopkins' strengths. I met some amazing mentors, clinicians, and researchers who got me excited about the potential for improving outcomes for patients with prostate cancer.

Back then, we knew very little about what made prostate cancer tick. We had very few effective treatment options. I felt like there was a lot to be done.

I also enjoyed the patient population of older men who brought to the table a lifetime's worth of experience and perspective, but who continued to have important aspirations and goals. I wanted to help them fulfill those goals.

> *"Molecular profiling is primarily limited to metastatic disease."*

What is genomics?

Dr. Alumkal: Genomics is the study of our DNA. In many ways, it's similar to genetics. When we think of genomics, we think of a much more comprehensive view of our DNA whereas genetics is a more focused or limited study of DNA.

Improvements in technology and in our ability to understand all of the DNA changes in a cell through the Human Genome Project were really transformational. Subsequently, the field came to understand that DNA sequencing technology that measures DNA changes could be incredibly useful in studying human disease and diseased tissues, including cancer. In the past two decades, there has been an explosion in our ability to study our DNA in a comprehensive, all-encompassing way. That is genomics.

How are we using—or not using—genomics in prostate cancer?

Dr. Alumkal: Currently, we are not using genomics for the screening or prevention of prostate cancer. Why? When we look at patients in the general population, the risk of having a heritable form of prostate cancer is quite rare. Most patients don't have a gene that runs in their family and is passed on to them that increases their own personal risk of prostate cancer. Population-based screening efforts to find individuals who have specific abnormal genes have therefore not occurred in prostate cancer.

It is more common to screen women with a very strong family history of breast or ovarian cancer for hereditary forms of disease genes like BRCA1 or BRCA2. The prevalence of those BRCA1 and BRCA2 mutations in men with prostate cancer is quite a bit lower. Therefore, there haven't been widespread efforts yet to detect those mutations by screening. Nor are there currently any approaches that target genomics or use genetic screening for prevention strategies.

As we understand more and more about genes that are abnormal in families with prostate cancer, particularly genes that might be more common, then we may develop screening efforts to identify at-risk families and family members of patients. But that won't happen until we have a better sense of how to approach cancers in individuals with specific abnormal genes.

We still don't know enough to make it useful?

Dr. Alumkal: That is a fair statement.

How do we use genomics to help men select the right initial treatment—surgery versus active surveillance, for example?

Dr. Alumkal: There are several tests on the market that help newly diagnosed patients make decisions.

Prolaris (https://prolaris.com/) is a test from a company called Myriad Genetics. Prolaris measures RNA not DNA. RNA is a message made from our DNA in our cells. Prolaris measures levels of genes important for controlling cancer cell growth and generates a cell cycle score. In prior work with Prolaris, researchers found that patients with aggressive, high Gleason grade cancers appear to have high levels of these genes important for cancer growth.

Men with a high Prolaris Cell Cycle Progression (CCP) score who were not treated with local therapy were also found to have an increased risk of death from prostate cancer.

Importantly, most of the patients with a higher Prolaris CCP score also had higher Gleason scores. That is to say, the test wasn't telling us a whole lot more than what we were already getting with the Gleason score.

Myriad then went on to look at the Prolaris CCP score in prostate cancer patients who opted for surgery. They used tissue from surgical samples and found that a higher Prolaris CCP score was associated with an increased risk of the cancer coming back—either a PSA recurrence or death from prostate cancer.

Additional data suggested that among men who choose radiation, those with a higher Prolaris CCP score might be more likely to have their cancer come back.

> *"Guardant Health has a blood-based assay for mutational profiling."*

Prolaris appears to be prognostic. It appears to give us information about who is likely to do worse than we thought, but it doesn't help us determine who can safely be observed or who needs treatment.

That is a critical distinction.

Based on the limited data that exists, we don't have sufficient information to say that a Prolaris CCP score can alter what we recommend for patients. But it can provide useful information to the clinician and patient above and beyond the clinical information we already have about how well or how poorly a patient might do.

Does that information then change the course of treatment?

Dr. Alumkal: Prolaris has primarily been used to predict outcome after treatment has already been completed. It doesn't offer much more information about how to approach that patient after treatment because it doesn't tell us what other therapies might make sense to reduce that patient's risk of having a bad outcome. Prolaris mainly provides information about whether that patient is at higher risk of recurrence than we thought. It doesn't give us clues about how to reduce that risk of recurrence.

What about Decipher?

Dr. Alumkal: There is another test called Decipher by GenomeDX (https://genomedx.com/). They studied the levels of genes in men who had surgery. They identified a 22-gene signature by measuring the levels of RNA in these samples. They found that certain genes are associated with an increased risk of the cancer coming back after surgery and leading to metastases. This test gives us a better sense of who is most likely to have their cancer come back after treatment.

They also evaluated Decipher in a small number of men undergoing salvage radiation. That study seemed to suggest that if you have a higher Decipher score, you're more likely to have your cancer return and to potentially pass away from your cancer despite salvage radiation therapy. That is one application of the Decipher test.

We need greater validation of this test in larger numbers of patients before we can determine that this test will tell us if salvage therapy after radical prostatectomy is likely to be helpful or not.

Again, if this test is implemented in a large number of patients in clinical trials and that effect still holds up, it could be quite promising. If a patient has an abnormal PSA after surgery, an important question is if the cancer is confined to the prostate area or is it elsewhere? Is salvage radiation likely to help, or is it likely to do nothing but cause side effects and do harm?

That is an example of how decision-making could be affected by test results.

What about OncoTypeDX?

Dr. Alumkal: OncotypeDX is a test by Genomic Health (http://www.genomichealth.com/). They have had a similar test for many years for breast cancer.

OncoType measures RNA levels or expression of genes. It was first developed on radical prostatectomy and biopsy samples. When they examined genes in biopsy samples from patients undergoing radical prostatectomy, they found high scores correlated with higher Gleason grades at the time of surgery and with a greater risk of the cancer not being confined to the prostate.

The value of OncoType is: you can look at a patient's biopsy, measure these genes, and get a better sense about the extent of the cancer at surgery than one might be able to predict by just looking at the biopsy, Gleason score, physical exam, and PSA.

They've also looked at OncoType in patients who have undergone surgery and have shown that higher OncoType scores are associated with an increased risk of recurrence.

Again, this test doesn't necessarily impact whether we treat patients or not or how specifically we treat them. We need larger validation studies to confirm that the test is useful in those terms.

As more data comes in from larger groups of patients and as we see these tests compared head to head, we'll be able to get a better sense of how and whether these molecular tests have a place in the management of patients with newly diagnosed prostate cancer.

Because they don't alter decision-making for the most part, but just provide prognostic information, we do not commonly use tests like Prolaris, OncoType, and Decipher in our practice here at OHSU.

What about molecular profiling tumors?

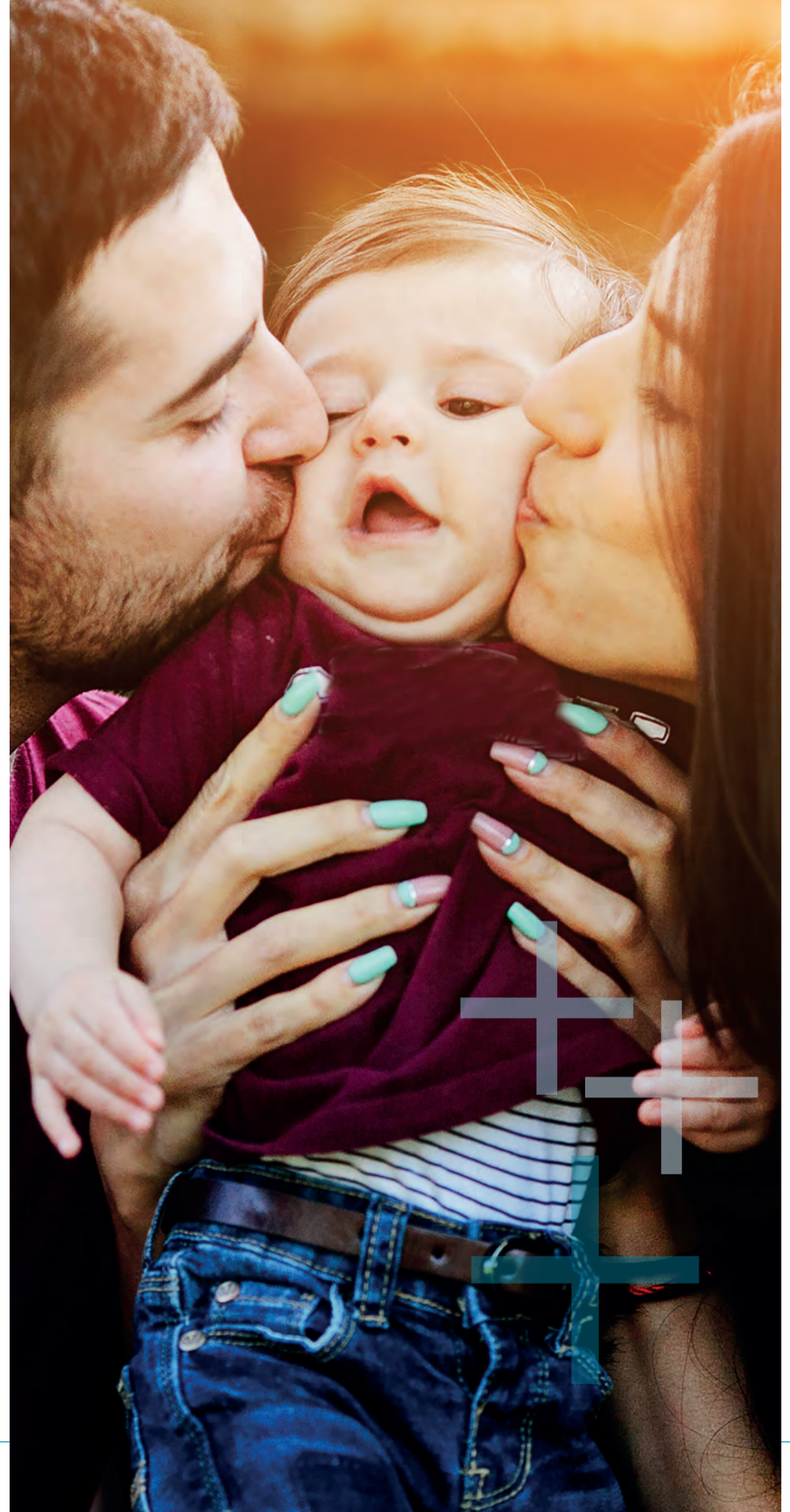
Dr. Alumkal: For patients with newly diagnosed localized prostate cancer, we have fairly standard therapies: radiation, surgery, hormonal therapy with radiation for higher grade cancers, hormonal therapy after surgery in patients who have lymph nodes involved, etc.

Otherwise, there isn't good data to suggest that the use of molecularly targeted therapy or any other forms of adjuvant therapy are useful to patients.

"Anything that doesn't kill a cancer makes it stronger."

Molecular profiling is primarily limited to metastatic disease. In that scenario, we're thinking more about how an abnormality may guide therapy. We think about using investigational agents, which are associated with risks and side effects. These investigational agents may be worthwhile because we think the benefit of treatment outweighs the risks.

For someone with localized prostate cancer, we don't know if finding specific molecular abnormalities will impact their care—particularly because local treatment with surgery or radiation may be sufficient to cure them. If we found a molecular abnormality in a localized prostate cancer, it would be a stretch to recommend an adjuvant molecularly targeted therapy.



Molecular profiling of a tumor certainly offers an opportunity to identify patients for clinical trials, but a lot of those efforts are focused on patients with advanced metastatic prostate cancer.

Would it make sense for men with metastatic disease to get their tumors molecularly profiled?

Dr. Alumkal: It's at least worth having a discussion with your physician about determining whether or not molecular testing is something that makes sense and if it could be done safely. Ideally, one would biopsy a new metastatic lesion rather than use an old, archived sample. That way you can get as much information as possible about what is going on at that point in time in a man's tumor.

AT OHSU, we have been involved with a Prostate Cancer Foundation and Stand Up to Cancer-funded Dream Team Award over the past three years. We routinely perform metastatic research biopsies in patients. We have an internal 124-gene mutation panel that we commonly perform in patients. That includes many gene alterations that are potentially targetable with specific drugs.

In our practice, the most common use of molecular testing is in patients who have advanced disease and whose cancers have progressed despite one or two approved therapies—when we're starting to run out of options.

We want to know if there are other things going on in the tumor that may be targetable with specific medications approved for diseases other than prostate cancer.

There has been a lot of excitement recently because a variety of groups have shown that approximately 20% of patients with metastatic prostate cancer resistant to most approved treatments have mutations in gene involved in DNA repair in their cancer. These mutations involve genes like BRCA1 or BRCA2, which are genes historically associated with hereditary forms of breast and ovarian cancers.

Preliminary data from a small clinical trial in the United Kingdom suggest that a class of medicines called PARP inhibitors—they specifically tested a drug approved for ovarian cancer called Lynparza (olaparib)—can work quite well in patients with mutations in these DNA repair genes. (See Prostatepedia June 2016 for a conversation with Dr. Joaquin Mateo about that study.)

That is one example of how a mutation found in molecular testing could lead us to recommend that certain patients join a clinical trial focused on PARP inhibitor treatment. A variety of companies that have developed PARP inhibitors have initiated, or will very soon initiate, clinical trials in men with advanced prostate cancer whose tumors have these abnormal genes.

That is an exciting new avenue of research—looking at tumors and finding abnormalities that seem to correlate well with response to a class of medicines. We have some sense of who may benefit from these drugs. But by no means do we know for certain all the patients who are likely to respond. There is some refinement needed in understanding which genes are really important and which patients may be best suited for that type of therapy.

This is one of the first examples of a molecular assay for prostate cancer that is being used to make treatment decisions for prospective clinical trials. It's a really exciting time, particularly since the frequency

of these alterations is around 20% and quite common.

If you do molecular profiling on one lesion in a man with multiple lesions, does that testing give you information about all of his lesions? Or does each individual lesion have its own molecular profile?

Dr. Alumkal: The verdict is still out on that. There are a variety of groups trying to tackle this question. Most of these studies have been done through what are called through rapid autopsies, in which patients donated their bodies to science to allow researchers to evaluate tumors from multiple sites.

There are certainly unique things that you will find in different metastases within a patient. In many cases, there are many features that are the same from metastasis to metastasis within the same patient.

There have been a small numbers of studies done in this area. Some work was done by Dr. Steven Bova in Finland and more recently in Dr. Peter Nelson's laboratory at Fred Hutchinson Cancer Research Center in Seattle, Washington.

Those studies have had some differing results. It is clear is that many of the alterations present within a patient are conserved across all their metastases. It's not uncommon when we treat patients with therapeutic drugs to see a fairly uniform response or progression in patients. Clinically, that does suggest that many drugs' behavior may be similar in different cancer lesions within a patient.

I think one way around what we call heterogeneity, or differences between tumor lesions within a patient, is to have tests that sample *all* of those tumors. That is where a lot of groups are developing blood-based sequencing or liquid biopsies. Tumors shed DNA into the circulatory system. You may be able to sample DNA and measure DNA from a variety of different tumor sites in a blood sample. This is another set of tests being developed by several companies. If those assays prove to be more helpful than a single biopsy of a single metastatic lesion, they may be useful in helping guide therapy.

Are liquid biopsies currently available?

Dr. Alumkal: There is at least one major company called Guardant Health (http://www.guardanthealth.com/), which has a blood-based assay for mutational profiling, including many of the genes relevant to prostate cancer involved in DNA repair. It is by no means a comprehensive set of genes, but that is probably the best known and most commonly used blood-based test on the market. There are several other companies developing tests similar to the Guardant assay that will soon be in this space.

There has really been an explosion in interest in trying to find non-invasive ways to sample tumors from patients and to provide molecular or genomic information. It's really hard to get sufficient material from metastatic biopsies to do genomic testing.

At OHSU, we have been fortunate enough to work with an excellent team of interventional radiologists who have honed their technique over the past several years. We're now at the point where the vast majority of biopsies we're performing provide sufficient tumor and DNA for informative molecular testing.

This is not something easily done at most centers. Having an expert radiology infrastructure is really critical. That is really why, hopefully, blood-based tests that can be done anywhere will be shown to be as effective, if not more so, than a single-site biopsy.

Are community oncologists and urologists interpreting and using this data effectively?

Dr. Alumkal: There are a variety of different companies that provide mutational testing. As I mentioned, we have our own diagnostic lab here at OHSU. Foundation Medicine (https://www.foundationmedicine.com/) is another company that provides these types of data. It is critical that the output of those tests and those reports be digestible, both by physicians who are at academic centers and by those in community practice. In many cases, patients themselves want these reports for their own records.

We need companies that can provide that information in a digestible fashion and provide recommendations on how those alterations may impact care and clinical trials. We need information that makes those genomic results most informative and actionable.

What are the barriers to genomics becoming more widely used to guide treatment?

Dr. Alumkal: Certainly cost, and whether payers will cover these tests, is critically important.

It will be important for the companies that develop these tests to demonstrate that mutational testing can have a significant impact on patient care and decision making. Those are open questions—whether or not the technology will provide better information than clinical information alone. If they can demonstrate impact that could certainly increase the usefulness of this information.

I think we need prospective cohorts of patients to demonstrate what these tests' characteristics are, what their false positives are, what their false negatives are, and how reliable they are. We want to know that if we were to order these tests, we're likely to find things that will impact how we care for patients.

Does it make any sense for a man five years after surgery to have tissue banked after biopsy or prostatectomy molecularly profiled?

Dr. Alumkal: If there isn't a new lesion that can be biopsied, one could consider using an old, archived sample from the same patient. Particularly if the patient has undergone multiple rounds of therapy that could dramatically alter the DNA of their tumor, then it's probably preferable to get a fresh biopsy and test that new tissue for gene alterations.

If that isn't possible, then I think there is value in going back and looking at that archived or prior specimen to see if something that was present then could be targetable or actionable. The hope would be that that abnormality is still present and that targeting it now with a specific medicine might make sense.

Those are obviously unknowns, particularly if five years have passed. We may have eradicated the tumor cell that was present to begin with in the original tumor sample and what has grown and emerged is an entirely different cell with a different set of alterations. That is why getting a fresh sample gives a better sense of what may be going on at this moment in time.

We've certainly had patients interested in getting more information about their tumor, particularly if they wanted to have as much information as possible to guide certain therapies. In those cases, we have gone back to those archive samples and tried to determine if there are abnormalities that were present that suggest a certain medication might make sense. In those cases, we refer patients for clinical trials, or in some cases prescribe medicines approved for other cancers to treat their disease.

Would it make sense to periodically redo molecular profiling as part of a monitoring plan or is that excessive?

Dr. Alumkal: Anything that doesn't kill a cancer makes it stronger. We know cancers continually evolve. My hope is that in the future, we'll get to the point where we can serially monitor patients with non-invasive blood tests to get a better sense of whether or not their treatment is working. If their treatment stops working: why? How has the cancer changed? To the extent that we can determine that that is safe and useful and can guide decision-making and treatment choices, then I think we'll see more widespread implementation of those sorts of tests.

It will take linking *finding* those abnormalities with *knowing* that if certain abnormalities are present certain medications may target those abnormalities. That will be paradigm-changing.

My hope is that in the very near future, we'll approach advanced prostate cancer the way oncologists approach localized breast cancer. Oncologists evaluate the estrogen receptor status, progesterone receptor status, and the HER2/NEU status to get a better sense of whether or not certain targets are present to guide whether certain therapies may work.

We've seen similar changes in lung cancer. If you have certain alterations in a gene called ALK or in a gene called the EGFR, then specific medications that target those abnormalities make sense for those patients.

We don't yet have those types of tests in prostate cancer, but I'm hopeful that through a variety of different research and commercial efforts we'll develop testing that can guide how we treat patients rather than the shot-in-the-dark approach we take now. Today, we just take existing drugs off the shelf and hope they'll work well in that specific patient sitting in front of us.

Don't you waste time and money in that approach?

Dr. Alumkal: Yes, because in many cases what we prescribe doesn't work and it takes time to figure that out. That is lost time for that patient who could have been on a more effective therapy or who could have avoided side effects. Getting more information about what is going on in the tumor and coupling that with therapies that can target the abnormalities present is a major unmet need in advanced prostate cancer specifically and in oncology in general.

Is there anything else you think prostate cancer patients should know?

Dr. Alumkal: We've never known more about prostate cancer than we do now in 2017. That will only improve. As we understand more about what makes each individual patient's cancer tick and as we find abnormalities that we can do something about, we'll really be able to make a significant difference in the lives of patients. I don't believe we're many years away from that. Pp1

Alicia Morgans, MD, MPH
Genomics In The Clinic

Dr. Alicia Morgans is a medical oncologist at Vanderbilt-Ingram Cancer Center in Nashville, TN. She specializes in treating advanced prostate cancer. She is particularly interested in addressing treatment side effects and in how men with advanced prostate cancer make treatment decisions.

Prostatepedia spoke with her recently about how genomics is—and isn't—being used in the clinic.

How did you come to focus on prostate cancer?

Dr. Alicia Morgans: I'm interested in prostate cancer for a number of reasons. First, I am very interested in understanding complications of cancer survivorship.

Prostate cancer is a disease for which we have been fortunate to have many new treatments emerge over the last few years. Men with prostate cancer, even advanced prostate cancer, are surviving for years on end. That gives us the opportunity to help make those years better, to understand the treatments that we're using, to understand the complications that we cause, and to think about how we can use those treatments in a way that minimizes complications.

The other reason is that my grandfather has had prostate cancer for a number of years.

It has been both professionally and personally very rewarding to be in the prostate cancer field.

What is genomics versus genetics?

Dr. Morgans: Genetics looks at different genes that can be passed on and inherited through different generations to give you certain traits or different features, like eye or hair color. Genomics for oncology is the study of the genes that alter a cancer's behavior or growth. It involves our understanding of what is driving a cancer's growth in a particular person.

Are we currently using genomics for screening prostate cancer?

Dr. Morgans: We use genetics in that we think about men with a first-degree relative with prostate cancer as being at higher risk. Some organizations suggest that men with a first-degree relative should start screening for prostate cancer at an earlier age, though with the United States Preventive Services Task Force (USPSTF) recommendations, things are a little bit murky right now.

> *"Advances in our understanding of genomics are definitely being integrated into clinical trial design."*

We think about people with a family history of breast and ovarian cancer who have BRCA1 and BRAC2 mutations as being an additional group who may think earlier about screening for prostate cancer. But we're not necessarily using genomics in the screening setting yet.

We use genomics after we have screened someone and taken a biopsy. Genomics can help us predict who may have an aggressive cancer and who may have a less aggressive cancer that can be followed with surveillance instead of treated immediately with surgery or radiation.

How are we using genomics to select initial treatments?

Dr. Morgans: There are some tests that men can use at the time of prostate cancer biopsy or after a prostatectomy that help them and

their doctors think about how likely their cancer is to come back, to become metastatic, or to cause them to die of prostate cancer. Those are tests urologists most commonly use.

"Sometimes we're limited by insurance."

Some are used when men get a biopsy and some, like the Decipher test, are used on a prostatectomy specimen. GenomeDX (https://genomedx.com/), the company that makes Decipher, just announced a biopsy product to predict the risk of metastatic disease, as well.

There is the Prolaris test (https://prolaris.com/) which is done on a biopsy specimen. Prolaris uses genomics to risk stratify who is likely to have their cancer come back in an aggressive form and who will have low-risk disease and not necessarily need to have surgery.

How do we use genomics to predict who will or will not respond to certain drugs? For example, looking at AR-V7 mutations to predict resistance to drugs like Xtandi (enzalutamide) and Zytiga (abiraterone)?

Dr. Morgans: AR-V7 testing, which would potentially help us predict who would respond to drugs like Xtandi (enzalutamide) or Zytiga (abiraterone), is not in clinical practice yet. We do not yet have a Clinical Laboratory Improvement Amendments (CLIA)-certified test that can identify AR-V7 mutations in circulating tumor cells or in prostate tissue that will tell us whether or not a patient will respond to Zytiga (abiraterone) or Xtandi (enzalutamide). At some point, a test like that will likely be commercially available.

There are clinical trials that are attempting to use the presence or absence of AR-V7 to either enroll people, risk stratify them, or statistically stratify them in the analysis, but it is not a commercially-available and clinically-used test at this point.

Do you think that is the path genomics will take in the future?

Dr. Morgans: We would love to have a test that could tell us which drugs will work for a particular patient's cancer and which drugs won't. We don't have those tests now, but if and when that information becomes available to clinicians, it will dramatically impact how we treat prostate cancer.

Do you think genomics will change how we design clinical trials?

Dr. Morgans: It already has to some extent. There are clinical trials that focus around certain mutations or alterations. There are studies that include only patients with AR-V7. There are PARP inhibitor studies that use the presence or absence of DNA repair defects to include or exclude patients. These advances in our understanding of genomics are definitely being integrated into clinical trial design. If those clinical trials demonstrate a benefit, it will be another step forward for genomics. Genomics will then have to be incorporated into our practice over time.

So it's just a matter of time before we demonstrate genomics' usefulness and then it will quickly become integrated into patient care?

Dr. Morgans: I don't know how quickly, but we're trying. Changing practices in medicine doesn't always move quickly enough for many of us for important safety reasons in place to protect patients. I would say that genomics has already demonstrated utility. Now we need to finish the clinical trials to really prove that it has a role in clinical practice to help men live longer and better lives. If the studies don't show this, it won't be integrated into patient care. I think we are all hopful that genomics will provide meaningful direction for clinicians as we choose among treatments for men with prostate cancer.

"Prostate cancers acquire new mutations."

To this point, there is a great *New England Journal of Medicine* paper by Dr. Joaquin Mateo and colleagues that performed biopsies on men with advanced disease who had had one or two lines of chemotherapy. (See *Prostatepedia* June 2016 for a conversation with Dr. Mateo about that study.)

The men in the study underwent biopsies and were then treated with Lynparza (olaparib), which is a PARP inhibitor. Those men who had DNA repair defect mutations appeared to have a very high response rate to Lynparza (olaparib) by the criteria included in that study.

I would say that genomics is already demonstrating the possibility of effectiveness. It just needs to be demonstrated on a larger scale. Mateo's study only included 50 or so people, not hundreds, as we would have in a definitive, practice changing study. But early signs of clinical utility are definitely there.

Couldn't a medical oncologist take that study by Dr. Mateo and his colleagues and apply the same principles to his or her own patient?

Dr. Morgans: Medical oncologists are doing that, but sometimes we're limited by insurance. I have patients on Lynparza (olaparib) right now, and we are hopeful that all will go well.

We commonly use genomic testing to look at mutations in patients' prostate cancers, but whether or not an insurance company will pay for us to use an off-label treatment is another question.

It's easier in a clinical trial setting, because pharmaceutical companies pay for the cost of the drug. It can be more challenging if you're not in a clinical trial setting.

Are those drugs very expensive?

Dr. Morgans: One of my patients paid out-of-pocket for a week for Lynparza (olaparib), and I believe it was in the thousands.

What about genomic tests? Are they expensive?

Dr. Morgans: That varies by state, by medical institution, and by patient insurance. I have not had trouble getting genomic testing for my patients.

What if a patient has already been treated years ago. Is the biopsy tissue usually preserved or does a patient have to request it?

Dr. Morgans: The patient doesn't have to request it if a biopsy or surgery was already done. The patient can talk to his doctor or his family could talk to his doctor and say, "We want to have genomic testing." The doctor just has to request the test and identify the tissue sample that should be used. Sometimes the patient has preserved samples. If that patient has had a prostatectomy, for example, there may be a recently preserved sample that could be sent.

However, I would say the most useful genomic testing is done on a metastatic site at the time that a patient is progressing after first line treatment. The reason is that over time, after being treated with multiple medications, prostate cancers acquire new mutations that allow them to become resistant to different treatments.

If you sample the initial prostate tumor, you may find a set of mutations that don't include the ones currently driving that cancer and allowing it to get around the treatments used at that particular time. If there is a way for patients to undergo a biopsy of a metastatic site, that tissue would give them a clearer picture of the mutational or genomic profile of his cancer at that time.

"Sometimes it takes a patient asking."

There can also be some difference, or heterogeneity, between the genomic profile of different metastatic sites. The genomic profile of one metastatic site may not be exactly the same as another metastatic site.

There are stronger driver mutations that we think really help that cancer grow and spread and are driving the growth of that cancer. We hope those mutations would be the same across different metastatic sites, but different sites do acquire different mutations. That has been demonstrated in multiple studies at this point.

If you get multiple biopsies over a number of years, should you have all of those tissue samples tested?

Dr. Morgans: You could. But I don't know how many times an individual insurance company will pay for genomic testing.

I have had some patients tested multiple times, usually separated by at least a year to two years because they were on one therapy and then another. These are not inexpensive tests. Sometimes an insurance company may say, "We just won't pay for that." But I have not had a problem getting a genomic test at least once for patients.

Is there anything else patients should know about genomics?

Dr. Morgans: Genomics is where we're going. Being able to predict who will respond to which treatment is our goal. We want to prevent people from being exposed to treatments that aren't going to help them and stop them from wasting time on therapies that are not going to help them to live longer and better lives.

I would say that, right now, while genomic testing is happening in the clinic, sometimes it takes a patient asking, "Can I have genomic testing on my tissue?"

If you are really interested in getting cutting edge prostate cancer treatments, at least understanding which mutations are present in your personal cancer is the place to start.

Jeffrey Swensen, PhD
Molecular Genetics + Prostate Cancer

Dr. Swensen is the Associate Director of Molecular Genetics at Caris Life Sciences in Phoenix, Arizona.

Prostatepedia spoke to him recently about hereditary prostate cancer and molecularly profiling.

How did you come to focus on molecular genetics?

Dr. Swensen: I wanted to be a pathologist, so I got a Bachelors degree in Medical Laboratory Science with cytotechnology specialization from the University of Utah. Cytotechnologists look at cells under the microscope—like pap smears for cancerous or precancerous changes.

Our lab got involved with a geneticist named Dr. Mark Skolnick who was interested in hereditary breast cancer. Dr. Scholnick was looking for pre-cancerous changes in the breasts of normal women from high-risk breast cancer families. I kept badgering him with questions. Finally, he asked, "Do you want to try doing molecular biology?" And offered me a job.

Dr. Mary-Claire King's group had found that some percentage of women who have a high risk of familial breast cancer all shared a piece of DNA on the long arm of chromosome 17. She didn't know what piece of DNA they shared or what the function was, but she knew that a lot of these women with a high hereditary risk of breast cancer all shared a common region.

Dr. Skolnick wanted to find that piece of DNA. Four years later, we found the BRCA1 gene and published. I was second author on the paper. He said I had enough for a PhD if I wanted to take the classes, so I became a geneticist.

I then worked at Myriad Genetics and helped them do diagnostics testing on the BRCA genes. I had spent a lot of time interpreting sequence variants.

Somebody with a PhD can become a Board-certified clinical geneticist to report DNA diagnostics cases. I did my Fellowship, passed the Boards, and started working as a clinical geneticist in a medical lab interpreting and reporting DNA diagnostic tests. When I saw an advertisement for a job at Caris Life Sciences focusing on cancer, I wound up here.

What do we know about inherited prostate cancer?

Dr. Swensen: Hereditary prostate cancer is messier than breast and ovarian cancer. There are highly penetrant genes that cause a high risk of breast cancer. People can get be tested for these genes and be readily counseled.

There aren't genes like that in prostate cancer. There are significant family risk factors involved in prostate cancer. If you are a man with a close relative with prostate cancer, your chance of having prostate cancer is increased. But there are not really strong genetic risk factors for prostate cancer that can be easily isolated like there are for breast cancer.

The most significant gene involved with hereditary prostate cancer predisposition is BRCA2. If you just look at random prostate cancers that come into a lab, a very small percentage will come from a BRCA2 mutation carrier. A male who has a BRCA2 mutation has an increased risk of getting prostate cancer. When these men do get prostate cancer, it's a more aggressive type more likely to metastasize and cause problems.

If you go back and look at aggressive metastatic prostate cancers, you'll find that probably 20% have mutations in BRCA2 or another gene in the same pathway (BRCA1, ATM). Some of those are mutations that have occurred only in the tumor. Some are germline, hereditary mutations. BRCA2 is quite a significant gene in determining if a prostate cancer is going to be aggressive and metastasize.

Again, a male with a BRCA2 mutation has an increased risk of getting prostate cancer, but it's not the same kind of risk a female BRCA2 carrier has of getting breast cancer. That is much more significant.

If a man reading this gets himself tested and discovers he is a BRCA2 carrier would that change his treatment path?

Dr. Swensen: It's actually useful information: 1) it means there' is a risk his tumor will be more aggressive; 2) those tumors are sensitive to the same sorts of agents, called PARP inhibitors, used to treat BRCA-positive ovarian cancers. The FDA has just approved PARP inhibitors for BRCA- and ATM mutation positive prostate cancers.

So if a man discovers he is a BRCA2 carrier would it be logical to go on a PARP inhibitor before another drug?

Dr. Swensen: There are still other lines of therapy that are pursued first, but PARP inhibitors have been quite effective in men with castration-resistant prostate cancers that have mutations in a BRCA gene or ATM.

Would it make sense for a newly diagnosed man to get himself tested for BRCA2?

Dr. Swensen: If you're just looking at all prostate cancers across the board, only 1% or 2% of patients have a BRCA mutation. I don't know about testing someone with a newly diagnosed localized prostate cancer, because there is only a fairly small chance that he will have a mutation.

If his cancer progresses or shows signs of being metastatic, then testing is definitely warranted.

What other kind of testing services does Caris Life Sciences offer for prostate cancer patients?

Dr. Swensen: We have a next-generation sequencing panel that includes a large number of genes involved in different kinds of cancer. We're looking for mutations that are potentially therapeutically significant.

When we look at prostate cancer, we're interested in seeing if there are pathogenic mutations in the BRCA or ATM pathway that will make that cancer sensitive to PARP inhibitors and platinum-based therapy.

As you know, patients typically begin with hormone-based therapy. Sometimes the cancer progresses on that hormone-based therapy. There can be various ways the tumor gets around hormone therapy, commonly involving the androgen receptor. Sometimes there will be point mutations in the androgen receptor. Sometimes the androgen receptor's RNA will be assembled together differently.

Is that the AR-V7 mutation?

Dr. Swensen: Exactly: AR-V7. We don't detect that right now, but we're setting up so that we can. Currently, we can see point mutations in the androgen receptor that are going to cause resistance to various therapies. Different point mutations that can occur in the androgen receptor interact differently with different hormone medications, so it's useful to know which point mutation is present.

We also offer a fusion panel that detects RNAs from different fusion genes. Fusion genes occur when chromosomes break and connect pieces of two different genes together to make a new gene.

About 50% of prostate cancers are driven by gene fusions. The most common is TMPRSS:ERG, which we can detect. Unfortunately, that is not therapeutically significant yet.

We also have pathologists who evaluate the tumors using immunohistochemical staining and other methods.

How do these tests fit in with other genomic testing?

Dr. Swensen: When we do our next-generation sequencing, we're only looking at DNA from tumors. When we find a mutation in a BRCA gene, for instance, we'll know that there is a BRCA mutation in the tumor and that is therapeutically significant. We'll put out a report that links that mutation to drug recommendations and possible clinical trials. But we won't know if that mutation is inherited or not. About half of the individuals with a BRCA mutation in their prostate cancer have inherited that mutation.

Only half?

Dr. Swensen: Yes. When we test advanced prostate cancers that have metastasized, we find that about 20% have a BRCA pathway mutation. About half of those are germline, or inherited, mutations. The other half are somatic mutations, or mutations that occur within the tumor. (Different studies report slightly different numbers.)

When we find a mutation, we know it's going to be therapeutically significant and can suggest that that man have further testing to find out if the mutation is inherited or not. That is where some of these other tests come in: they do germline, or inherited mutation, testing. They can find out if that person has that mutation in every cell of their body—if it's an inherited mutation. And if it is, other family members are also at risk. Pp[1]

Clinical Trial:
Kosj Yamoah, MD, PhD
Decipher + African American Men

Dr. Kosj Yamoah is an Assistant Professor in the Department of Radiation Oncology & Cancer Epidemiology of the Genitourinary Oncology Program at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida. He is particularly interested in prostate cancer disparity in men of African descent.

"Two populations on two separate continents with a common ancestry have a common disease."

Prostatepedia spoke with him recently about his clinical trial on Decipher use in African American men.

How did you come to focus on prostate cancer?

Dr. Kosj Yamoah: Most of my mentors during my years of training as a physician-scientist happen to be in the prostate cancer field; they drove my initial interest in prostate cancer.

My interest was further fine-tuned by the fact that as an African American physician actively involved in the management of prostate cancer patients, I witnessed the disproportionate severity of disease burden of prostate cancer among African American men, as well as in men living in Africa and in the Caribbean. I truly appreciate the importance of additional research in this field with the goal of improving outcomes in this patient population. Prostate cancer has become a unifying and rewarding career path for me. I find myself working on a problem that is near and dear to my heart.

What is the Decipher test?

Dr. Yamoah: Decipher is a genomic test that looks at the extent of the mutational burden within a tumor tissue taken during prostate biopsy or surgery. We're able to use that expression pattern of specific genes to predict the probability of a patient developing metastatic disease down the line. It measures the expression levels of 22 RNA biomarkers involved in multiple biological pathways across the genome associated with aggressive prostate cancer.

Is Decipher used to guide prostate cancer treatment?

Dr. Yamoah: Decipher has made its transition into the clinic as a prognostic tool. Currently, Decipher

is used by many major academic centers to help guide some management decisions. It is recommended in the National Comprehensive Cancer Network (NCCN) guidelines for the management of prostate cancer, but the uptake in the community has been a lot slower.

What is the thinking behind your clinical trial?

Dr. Yamoah: Across the board, many of these prognostic and/or predictive tools for prostate cancer have by and large been derived from tumor tissue from non-African American patients, mainly Caucasian patients. That has created a rich knowledge of prostate cancer, but only represents a sub-population of the United States.

If we think about the fact that overall men of African descent or African American men have a 1.6-fold incidence of prostate cancer and are 2.4-fold more likely to die from prostate cancer, it is almost unreal that we don't have enough tissue samples for genomic studies to see what kind of biologic process is being co-opted in these aggressive types of prostate cancer.

Is that increase in incidence and in death all explained through access and economic status? Could it be a biological difference? The way I look at it is this: it is perhaps easy to explain increased death by saying these men didn't get treated or weren't diagnosed early enough, but it's very hard to explain incidence, meaning an increased number of men who get prostate cancer, across a sub-population just by access. That is not simply an access issue. There may be a biologic process involved in the observed disparity in incidence and mortality.

When we recognize that prostate cancer is the second leading cause of cancer mortality among men living on the African continent, it speaks more to biology: two populations on two separate continents with a common ancestry have a common disease. That then becomes an important area to study.

In the last decade, studies have changed the landscape for screening men at increased risk of prostate cancer. Some experts say that screening doesn't change overall outcomes, so we shouldn't screen men for prostate cancer. But we are beginning to see late diagnosis because of lack of screening with potentially disproportionate effects in African American men who were not, for the most part, included in the original studies.

All of this together gave birth to the study.

What should patients expect to happen during the study?

Dr. Yamoah: We are enrolling African Americans on a rolling basis. We are using a validated tool called the CAPRA score. We will take a one time blood sample and tumor tissue sample for genomic analysis and Decipher testing.

We will get over 1.4 million transcripts of genomic data through the Decipher Genomic Resource Information Database (GRID). We will then begin to correlate that genomic data with the biology of the disease as estimated by time to biochemical recurrence, meaning from time of treatment to when the patient's PSA starts to rise.

We can then begin to identify pathways or targets for subsequent studies so that we can intensify treatment in patients who do need intensive treatment and de-intensify treatment methods for patients who don't.

Are there any other eligibility requirements?

Dr. Yamoah: We are focusing on patients with high volume, low-risk prostate cancer. We want patients who haven't been treated with something else before coming for definitive treatment. We don't want to interfere with their treatment choice.

Patients do not need to be treated at the Moffitt Cancer Center, but can be treated anywhere.

Is there anything else you think patients should know about genomics or about this study in particular?

Dr. Yamoah: Patients should ask their providers if they qualify for genomic testing. The subset of patients eligible for Decipher testing should be offered the opportunity, because it could potentially increase our knowledge of prostate cancer as well as impact the treatments the patient receives down the line. Pp[1]

How To Get Involved…

Patients who are interested in participating should call Moffitt Cancer Center at (813) 745-2588.

Prostatepedia[1]
[1]expert insight + advice

Patients Speak
Mr. Philip Steward: Pursuing Genomic Testing

Mr. Philip Steward is on the Steering Committee for two San Francisco Bay area support groups.

Prostatepedia spoke with him recently about his experiences with prostate cancer molecular profiling.

How did you find out that you had prostate cancer?

Mr. Philip Steward: I had a rising PSA for several years at my annual physical. The doctor kept saying we won't worry about this until your PSA gets to 10.

In 2001, I told my general practitioner that I wanted to have a urologist take a look. The urologist did a DRE and immediately said I should have a biopsy. I was then diagnosed with Gleason Grade score 8 prostate cancer. Sixty percent of my biopsy cores were positive. My PSA was 3.85.

If I had waited until that PSA got to 10, I might not be talking to you right now.

The urologist, of course, was a surgeon. He recommended surgery and said that guys like me—with my numbers—typically live seven years.

I asked him what the chances were that the cancer had already escaped the prostate. He said about 60%. I asked then why would you do a local therapy? He said you either beat this stuff or you don't. Of course, it was devastating.

"If I had waited until that PSA got to 10, I might not be talking to you right now."

But that's when I decided to get educated.

How did you find your support group?

Mr. Steward: Two good friends of mine had had prostate cancer earlier. I called them both two days after I got the pathology report. One suggested a support group in Mountain View, California, near where I live.

How did you come to use molecular profiling for your prostate cancer?

Mr. Steward: My first approach was to make an appointment with Dr. Leibowitz and his associate Dr. Tucker. They prescribed hormonal therapy and concurrent low dose chemotherapy. The chemotherapy consisted of five cycles. Each cycle included chemotherapy infusions every week for three weeks followed by a week off.

After this series of chemotherapy and hormonal therapy, I had no treatment for the following five years during which time my PSA slowly returned. I then went on hormonal therapy again for nine months. I was treatment-free for two years. Once again, the PSA slowly returned.

When the PSA came back again, I saw Dr. Mac Roach at the University of California, San Francisco (UCSF) to have IMRT radiation to my pelvic area and high-dose radiation to my prostate gland itself.

After the radiation treatments, another five years passed without any treatment, but my PSA slowly rose again. At that point I had a multiparametic MRI at UCSF along with a biopsy of my prostate. They didn't find any cancer.

A little over a year ago, I went to Phoenix Molecular Imaging in Phoenix, Arizona for a C11-acetate PET/CT scan. They found that my pelvic area and abdomen were clear. The radiation treatments had been successful. But now I had metastasized cancer in my lungs—20 nodules.

I wanted to make sure that the nodules were really prostate cancer, so Dr. Steven Schwartz at Good Samaritan Hospital in San Jose, California was able to obtain tissue samples of the nodules using a video-assisted thoracoscopic surgery (VATS) procedure. The pathology of the lung nodules proved it was really prostate cancer.

I requested the tissue samples be sent to Foundation Medicine (https://www.foundationmedicine.com/), hoping to find out if I would be taxane-sensitive. Foundation Medicine was not able to tell me if my cancer was taxane-sensitive.

I then learned that GenomeDX (https://genomedx.com/) in San Diego could test to determine taxane sensitivity. I contacted them and submitted a sample of my lung tissue for evaluation. They sent the results to Dr. Tanya Dorff at the University of Southern California-Norris Cancer Center who thought the metastasized cancer would be sensitive to Taxotere (docetaxel) and that I didn't need Paraplatin (carboplatin) as a part of my infusion treatment. She thought there was an overexpression of two genes for which existing drugs might be effective if the chemotherapy didn't work.

You took the initiative to contact GenomeDX? Your doctor didn't suggest it?

Mr. Steward: Right. My doctor really didn't know that they could do that kind of testing.

A representative of GenomeDx, Jason Alter, spoke to our San Jose, California support group. He said they could test for taxane-sensitivity.

"Of course, it was devastating. But that's when I decided to get educated."

The test isn't FDA-approved, so it would cost money. I emailed the company and they said it would cost $3100 to test a sample of my lung tissue.

Is it normally covered by insurance?

Mr. Steward: No. It is not covered by insurance.

Did you talk to other patients in your support group about your experiences?

Mr. Steward: I talked to everyone in my support group. No one has used this kind of testing.

"There are several men in the group who probably know more about prostate cancer than my general practitioner did at the time of my diagnosis."

Because their doctors hadn't suggested it? Or they're reluctant ?

Mr. Steward: Probably because their current circumstances don't present a need for this information.

You have taken a proactive approach, haven't you?

Mr. Steward: I felt I had to. Gleason grade score 8 is not trivial.

Are you still an active member of the Mountain View support group?

Mr. Steward: I'm on the Steering Committees for both the Mountain View, California group and the San Jose, California group.

I suppose you would never have known about GenomeDX without the support group.

Mr. Steward: I went to a support group meeting two days after being diagnosed and found the level of knowledge possessed by the members impressive. There are several men in the group who probably know more about prostate cancer than my general practitioner did at the time of my diagnosis.

Do you have any advice for men considering this kind of testing?

Mr. Steward: If you were considering chemotherapy, it would be nice to know if your tumor is going to be sensitive to it, because the side effects are really harsh. I have been told that about half of men with prostate cancer don't have a form of cancer that is sensitive to taxane-based chemotherapy. Since 100% of men have the side effects, half the men suffer for no benefit.

A series of chemotherapy infusions is expensive. It would be more cost-effective for your insurance company to pay $3100 to test for chemotherapy sensitivity than to pay for chemotherapy that doesn't work. If I were facing chemotherapy and had the money, I would get my tumor tested to make sure it was Taxotere (docetaxel)-sensitive. Pp!

ONCE-DAILY
Xtandi®
(enzalutamide)
40 mg capsules

XTANDI takes on advanced prostate cancer while you take on what matters to you.

Who is XTANDI for? XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body.

FIND OUT HOW YOU CAN FIGHT BACK.
Talk to your doctor and visit XTANDI.com/info

Important Safety Information

Who should not take XTANDI?

XTANDI is not for use in women. Do not take XTANDI if you are pregnant or may become pregnant. XTANDI can harm your unborn baby. It is not known if XTANDI is safe and effective in children.

Before you take XTANDI, tell your healthcare provider if you:

- Have a history of seizures, brain injury, stroke or brain tumors.
- Have any other medical conditions.
- Have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form of birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See "Who should not take XTANDI?"
- Take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works. You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

How should I take XTANDI?

- XTANDI is four 40 mg capsules taken once daily.
- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.
- If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure. Your healthcare provider will stop XTANDI if you have a seizure during treatment.
- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

The most common side effects of XTANDI include weakness or feeling more tired than usual, back pain, decreased appetite, constipation, joint pain, diarrhea, hot flashes, upper respiratory tract infection, swelling in your hands, arms, legs, or feet, shortness of breath, muscle and bone pain, weight loss, headache, high blood pressure, dizziness, and a feeling that you or things around you are moving or spinning (vertigo).

XTANDI may cause infections, falls and injuries from falls. Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see the Brief Summary on the following page and the Full Prescribing Information on XTANDI.com.

QUESTIONS ABOUT XTANDI? | **Call 1-855-8XTANDI (1-855-898-2634)**

astellas MEDIVATION

Xtandi® (enzalutamide) capsules 40mg

PATIENT INFORMATION
XTANDI® (ex TAN dee)
(enzalutamide)
capsules

What is XTANDI?

XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body.

It is not known if XTANDI is safe and effective in children.

Who should not take XTANDI?

XTANDI is not for use in women.
Do not take XTANDI if you are pregnant or may become pregnant. XTANDI can harm your unborn baby.

What should I tell my healthcare provider before taking XTANDI?

Before you take XTANDI, tell your healthcare provider if you:

- have a history of seizures, brain injury, stroke, or brain tumors
- have any other medical conditions
- have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form of effective birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See "**Who should not take XTANDI?**"

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XTANDI?

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- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
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- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.
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What are the possible side effects of XTANDI?

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- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

The most common side effects of XTANDI include:

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- back pain
- decreased appetite
- constipation
- joint pain
- diarrhea
- hot flashes
- upper respiratory tract infection
- swelling in your hands, arms, legs, or feet
- shortness of breath
- muscle and bone pain
- weight loss
- headache
- high blood pressure
- dizziness
- a feeling that you or things around you are moving or spinning (vertigo)

XTANDI may cause infections, falls and injuries from falls. Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XTANDI?

- Store XTANDI between 68°F to 77°F (20°C to 25°C).
- Keep XTANDI capsules dry and in a tightly closed container.

Keep XTANDI and all medicines out of the reach of children.

General information about XTANDI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XTANDI for a condition for which it was not prescribed. Do not give XTANDI to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about XTANDI. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about XTANDI that is written for health professionals.

For more information go to www.Xtandi.com or call 1-800-727-7003.

What are the ingredients in XTANDI?

Active ingredient: enzalutamide

Inactive ingredients: caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, black iron oxide

Manufactured by:
Catalent Pharma Solutions, LLC, St. Petersburg, FL 33716

Marketed by:
Astellas Pharma US, Inc., Northbrook, IL 60062
Medivation Inc., San Francisco, CA 94105
14L082-XTA-BRFS

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: August 2015

WHAT IS ZYTIGA® (abiraterone acetate)?

ZYTIGA® is a prescription medicine that is used along with prednisone. ZYTIGA® is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

IMPORTANT SAFETY INFORMATION

Who should not take ZYTIGA® (abiraterone acetate)?

Do not take ZYTIGA® if you are pregnant or may become pregnant. ZYTIGA® may harm your unborn baby. Women who are pregnant or who may become pregnant should not touch ZYTIGA® without protection, such as gloves.

ZYTIGA® is not for use in women or children. **Keep ZYTIGA® and all medicines out of the reach of children.**

Before you take ZYTIGA®, tell your healthcare provider if you:

- Have heart problems
- Have liver problems
- Have a history of adrenal problems
- Have a history of pituitary problems
- Have any other medical conditions
- Plan to become pregnant **(See "Who should not take ZYTIGA®?")**
- Are breastfeeding or plan to breastfeed. It is not known if ZYTIGA® passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA® or breastfeed. You should not do both. **(See "Who should not take ZYTIGA®?")**
- Take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZYTIGA® can interact with many other medicines.

If you are taking ZYTIGA®:

- Take ZYTIGA® and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA® one time a day. Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA® or prednisone without talking to your healthcare provider first.
- Take ZYTIGA® on an empty stomach. **Do not take ZYTIGA® with food.** Taking ZYTIGA® with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA®.
- Swallow ZYTIGA® tablets whole. Do not crush or chew tablets.
- Take ZYTIGA® tablets with water.
- Your healthcare provider will do blood tests to check for side effects.
- Men who are sexually active with a pregnant woman must use a condom during and for one week after treatment with ZYTIGA®. If their female partner may become pregnant a condom and another form of birth control must be used during and for one week after treatment with ZYTIGA®. Talk with your healthcare provider if you have any questions about birth control.
- If you miss a dose of ZYTIGA® or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.

ZYTIGA® may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia), and fluid retention (edema).**

Tell your healthcare provider if you get any of the following symptoms:

- Dizziness
- Feel faint or lightheaded
- Confusion
- Pain in your legs
- Fast heartbeats
- Headache
- Muscle weakness
- Swelling in your legs or feet

- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems.** You may develop changes in liver function blood tests. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA® and during treatment with ZYTIGA®. Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - Yellowing of the skin or eyes
  - Darkening of the urine
  - Severe nausea or vomiting
- The most common side effects of ZYTIGA® include:
  - Weakness
  - Joint swelling or pain
  - Swelling in your legs or feet
  - Hot flushes
  - Diarrhea
  - Vomiting
  - Cough
  - High blood pressure
  - Shortness of breath
  - Urinary tract infection
  - Bruising
  - Low red blood cells (anemia) and low blood potassium levels
  - High blood sugar levels, high blood cholesterol and triglycerides
  - Certain other abnormal blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

THESE ARE NOT ALL THE POSSIBLE SIDE EFFECTS OF ZYTIGA®.

FOR MORE INFORMATION, ASK YOUR HEALTHCARE PROVIDER OR PHARMACIST.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ZYTIGA® can interact with other medicines.

You should not start or stop any medicine before you talk with the healthcare provider who prescribed ZYTIGA®.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

Call your doctor for medical advice about side effects. You are encouraged to report negative side effects of prescription drugs to the FDA.

Visit www.fda.gov/medwatch, or call 1-800-FDA-1088 (1-800-332-1088).

051527-160418

Janssen Biotech, Inc.
800 Ridgeview Drive
Horsham, PA 19044 USA

08/16 038767-160817

janssen

PATIENT INFORMATION
ZYTIGA® (Zye-tee-ga)
(abiraterone acetate)
Tablets

Read this Patient Information that comes with ZYTIGA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ZYTIGA?
ZYTIGA is a prescription medicine that is used along with prednisone. ZYTIGA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

ZYTIGA is not for use in women.

It is not known if ZYTIGA is safe or effective in children.

Who should not take ZYTIGA?
Do not take ZYTIGA if you are pregnant or may become pregnant. ZYTIGA may harm your unborn baby.

Women who are pregnant or who may become pregnant should not touch ZYTIGA without protection, such as gloves.

What should I tell my healthcare provider before taking ZYTIGA?
Before you take ZYTIGA, tell your healthcare provider if you:
- have heart problems
- have liver problems
- have a history of adrenal problems
- have a history of pituitary problems
- have any other medical conditions
- plan to become pregnant. See "**Who should not take ZYTIGA?**"
- are breastfeeding or plan to breastfeed. It is not known if ZYTIGA passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA or breastfeed. You should not do both. See "**Who should not take ZYTIGA?**"

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZYTIGA can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed ZYTIGA.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take ZYTIGA?
- Take ZYTIGA and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA 1 time a day.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA or prednisone without talking with your healthcare provider first.
- Take ZYTIGA on an empty stomach. **Do not take ZYTIGA with food.** Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA.
- Swallow ZYTIGA tablets whole. Do not crush or chew tablets.
- Take ZYTIGA tablets with water.
- Men who are sexually active with a pregnant woman must use a condom during and for 1 week after treatment with ZYTIGA. If their female partner may become pregnant, a condom and another form of birth control must be used during and for 1 week after treatment with ZYTIGA. Talk with your healthcare provider if you have questions about birth control.
- If you miss a dose of ZYTIGA or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.
- Your healthcare provider will do blood tests to check for side effects.

What are the possible side effects of ZYTIGA?
ZYTIGA may cause serious side effects including:
- **High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema)**. Tell your healthcare provider if you get any of the following symptoms:
  - dizziness
  - fast heartbeats
  - feel faint or lightheaded
  - headache
  - confusion
  - muscle weakness
  - pain in your legs
  - swelling in your legs or feet
- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems**. You may develop changes in liver function blood test. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA.
  Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - yellowing of the skin or eyes
  - darkening of the urine
  - severe nausea or vomiting

The most common side effects of ZYTIGA include:
- weakness
- joint swelling or pain
- swelling in your legs or feet
- hot flushes
- diarrhea
- vomiting
- cough
- high blood pressure
- shortness of breath
- urinary tract infection
- bruising
- low red blood cells (anemia) and low blood potassium levels
- high blood sugar levels, high blood cholesterol and triglycerides
- certain other abnormal blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ZYTIGA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZYTIGA?
- Store ZYTIGA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ZYTIGA and all medicines out of the reach of children.

General information about ZYTIGA.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ZYTIGA for a condition for which it was not prescribed. Do not give ZYTIGA to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about ZYTIGA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZYTIGA that is written for health professionals.

For more information, call Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or go to www.Zytiga.com.

What are the ingredients of ZYTIGA?
Active ingredient: abiraterone acetate

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

Manufactured by: Patheon Inc. Mississauga, Canada
Manufactured for: Janssen Biotech, Inc. Horsham, PA 19044

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: May 2016

051810-160421

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Redwood City, CA 94065
434-220-3774
info@prostatepedia.net
www.prostatepedia.net

Coming Up!

April
Bone Metastases

May
Collaborations

June
Prevention and Screening

July
Advances In Treatment