Prostatepedia[1]

[1]expert insight + advice

Testing

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In this issue....

This issue represents a rather detailed look at the current state of blood and tumor tissue testing in prostate cancer. The PSA is the classic example against which new tests can be compared. The PSA is largely useful in so far as the measured value is proportional to the total mass of prostate tissue, normal plus malignant. As a screening tool, PSA elevation can signal the presence of cancer and the PSA rate of increase can reflect the pace of cancer growth.

Unfortunately, other processes, such as prostatitis, can also cause PSA elevation and aggressive cancers can make less PSA per gram of tissue. These factors have limited the value of the PSA for screening.

For patients who are post prostatectomy or radiation therapy, there are fewer issues and the PSA doubling time is a widely used prognostic indicator for patients with recurrent disease.

How do the other tests discussed in this issue act to provide additional or more accurate information about prostate cancer?

Genomic tests can provide information on important functional differences between normal tissue and cancer. Perhaps the best example of this are mutations in the DNA repair genes, BRCA2 and ATM. Germline mutations in these genes increase the risk of prostate cancer and the resultant cancers tend to be more aggressive. These mutations can also develop as prostate cancer progresses and have been observed in 20-30% of hormone resistant cases.

Furthermore, cancer cells bearing these mutations are more likely to respond to drugs that inhibit PARP, a different DNA repair protein. Thus, testing for BRCA2 or ATM tells us about changes in the cancer's ability to repair DNA damage, shed light on the risk of aggressive disease, and help select effective treatment. Tests like these that reveal functional differences between normal and cancer cells have great promise to improve treatment of prostate cancer. This approach has already been successfully applied to other cancers, such as non-small cell lung cancer, where it has revolutionized treatment.

Genomic changes need not be assessed at such a focused fashion as is done with BRCA2. Instead, multigene DNA, RNA, or protein patterns can be measured and tested for their ability to predict cancer aggression or response to standard therapy. Examples of this approach include the Decipher, Oncotype Dx, and Prolaris tests.

These tests can be viewed as supplementary to or even competitive with standard histologic evaluation by a pathologist. This has naturally led to some controversy about their role. In this issue, Dr Epstein does an effective job critically comparing histology versus the genomic approach. In my view, the relative role of the two ways of assessing future cancer behavior is still very much an open issue.

We hope you enjoy this issue as much as we have enjoyed putting it together.

Charles E. Myers, Jr., MD Pp

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Introduction from Merel Grey Nissenberg President, NASPCC

NASPCC is thrilled to publish this March issue of *Prostatepedia* Magazine on the topic of "TESTING."

This is not your standard collection of information on testing in general, long a topic of meetings, lectures, and the literature. This is a unique gathering of stellar experts whose interviews cover new types and topics in testing and novel approaches allowing precision therapies to be employed based upon the results of those new types of tests.

From Dr. Jonathan Epstein, renowned urological pathologist in prostatic and bladder diseases at Johns Hopkins, discussing the new Gleason Scoring System and the role of pathologists in this disease; to Dr. Ashley Ross at Northwestern Medicine discussing genomic tests in localized prostate cancer and especially the Genomic Classifier score (with its 22-gene panel) from Decipher; to Dr. Robert Reiter at UCLA discussing exosome urine-based testing: we cover a lot of material. Our Editor, Jessica Myers-Schecter, also interviewed Dr. Scott Tomlins of Strata Oncology and the University of Michigan on genomic testing for metastatic disease; Dr. Jeffrey Ross of Foundation Medicine regarding genetic and genomic testing, companion diagnostics, and PARP Inhibition; and Sam Salman, CEO of miR Scientific, about their FDA-designated breakthrough urine-based liquid biopsy test for the detection and risk classification of prostate cancer. Last but not least, Victor Ortiz describes his journey as a prostate cancer patient learning about his genetic variants that ultimately helped determine what treatments to undergo. We hope the informative solidity of this issue, along with the "Flipping-Book" version for ease of reading, will show once again that *Prostatepedia Magazine* (along with the weekly *Prostatepedia Digest*) is an important resource for men and their families dealing with prostate cancer. Pp!

"This is not your standard collection of information on testing."

Report from ASCO 2021

Merel Grey Nissenberg

President, NASPCC

ASCO GU is a yearly multidisciplinary symposium with world-renowned faculty that covers relevant topics in genito-urinary malignancies. Both state-of-the-art tests and treatments, as well as new research, were presented virtually this year. Here is a report on some of the more important presentations in prostate cancer.

Dr. Peter Carroll of UCSF gave a 2021 update on active surveillance (AS), which is traditionally used in low-low risk, low-risk, and favorable intermediate-risk prostate cancer to help avoid overtreatment. Its use, however, varies widely across the country. The cautionary worry with Active Surveillance is that men will progress (be upgraded to a worse Gleason Grade Group or worse situation with long-term use). Dr. Carroll spoke of the genomic profiling that can be done for these patients; for example, the use of GPS (Oncotype Dx) combined with a CAPRA Score can help predict adverse events. That kind of data can reveal if there is an increased risk or a decreased risk of an upgrade in disease extent; but he cautioned that the data is not absolute in and of itself, and must be used in context. Dr. Carroll said that there are several indications in considering the appropriateness of AS, including age, PSA Density (PSAD) less than .15; 2 negative biopsies; serial MRI's (if the patient is not going to have a biopsy), Grade and volume. Dr. Carroll also spoke to controversies with AS, for example, should younger patients be enrolled? He said that younger men on AS actually have a lower rate of progression. In describing pathology, he said that Gleason Grade alone is not predictive but that volume is, and that with Grade Group 4 the presence of cribiform and stromal reaction are in fact correlated with progression. One must also be careful with patients with a positive BRCA2 mutation. Also, Dr. Carroll stated that while African American patients do not appear to have different results with AS, he said that they represent only a small proportion of patients in these cohorts of the pertinent trials. However, Dr. Carroll cautioned that AS needs to become less burdensome for greater use.

Dr. Felix Feng, also of UCSF, addressed molecular signatures associated with long-term response to apalutamide in nonmetastatic castration-resistantprostate cancer (nmCRPC). This was a new analysis of findings from the SPARTAN Trial, a Phase III trial which evaluated the efficacy of apalutamide in combination with ADT in patients whose disease had become resistant to hormonal therapy but who did not have metastatic disease. The primary endpoint was metastases-free survival (MFS). SPARTAN's final analysis showed an overall survival benefit to the apalutamide group of 73.9 months versus 59.9 months in the placebo group. In the current analysis, Dr. Feng separated Time-to-Progression events into quartiles, defining Long-Term Responders (LTRs) as those without events until the 4th quartile, and Early Progressors (EPs) having events in the first quartile. In the apalutamide + ADT group, increased immune activity, or decreased vascularization or proliferative capacity at baseline were associated with LTR. He also mentioned that luminal tumors typically have a better MFS than basal tumors treated with APA + ADT, unless those basal tumors have a high T-cell proliferation.

Dr. Jonathan Tward of the Huntsman Cancer Institute at the University of Utah presented the results of a study showing that a score based upon clinical characteristics along with cell cycle proliferation (CCP) gene expression can provide accurate information on prognosis in terms of the 10-year risk of metastasis in patients with intermediate- and high-risk localized prostate cancer. The combined clinical and cell-cycleRisk (CCR) score combines a CCP Score from Myriad's Prolaris test (31 CCP genes) with clinical indications. This was a validation study; a prior development study had found that a CCR score cutoff of 2.112 could identify patients who had less than a 5% risk of metastasis at 10 years, regardless of use of ADT or NCCN risk group. Thus, importantly, those patients with a risk of metastasis less than 5% can be counseled that the use of ADT may not be clinically significant, thereby avoiding its use.

Good news from the radiation therapy and theranostics field: The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) announced results of the TheraP Trial, which compared 177Lu-PSMA-617 (Lu-PSMA), a novel radioactive treatment, to the current standard-of-care chemotherapy (cabazitaxel) for men with metastatic castration-resistant prostate cancer. This study utilized theranostics, first mapping the cancer with a PET scan, and then treating the men with radioactive Lutetium-177 attached to a similar molecule as that used for the PET scan. The primary endpoint was to assess change in PSA following treatment; a favorable response was defined as a reduction in PSA of 50% or more. This reduction occurred in 66% of the men who received Lu-PSMA compared to 37% in those men who received cabazitaxel. The Lutetium patients also had fewer adverse events than the Cabazitaxel group. Chair Professor Ian Davis said that "TheraP is the first trial in the world comparing

Lu-PSMA to an active and effective treatment and has provided evidence that Lu-PSMA might be a good alternative option to chemotherapy for men with advanced and pretreated prostate cancer."

And again, in a plenary abstract in the Poster Highlights Session, a report was made on a prospective Phase II/III Study of PSMA-targeted 18F-DCFPyl -PET/CT in patients with prostate cancer (OSPREY). PSMA imaging is very promising for prostate cancer detection, with higher sensitivity, specificity, and accuracy. 18F-DCFPyL is a new PSMA-targeted radiopharmaceutical for PET; on the basis of the data presented, it was concluded that "18F-DCFPyL-PET/CT may be a useful tool in staging men with both metastatic and nonmetastatic relapsed prostate cancer." And in a separate presentation entitled the "Wild West," Dr. Declan Murphy of Australia expounded on how outstanding PSMA-Gallium (just approved in the US) is for imaging in prostate cancer. In Australia they have been using it for six years.

In the field of testing, Foundation Medicine and collaborators announced that a new study continued to demonstrate the clinical utility of blood-based comprehensive genomic profiling (CGP) in patients with advanced prostate cancer. Their study evaluated genomic alterations which were identified using liquid biopsy in over 3,000 patients, and also looked at concordance with liquid and tissue biopsy in over 800 patients. There was high concordance between targetable alterations utilizing circulating tumor DNA (ctDNA) and tissue-based CGP in patients with metastatic castrate-resistant prostate cancer. In many patients, it was found that liquid biopsy detected more acquired resistance mechanisms than were detected by tissue biopsy. Dr. Geoff Oxnard of Foundation Medicine stated "When tumor tissue is difficult to obtain, as is often the case in patients in mCRPC, liquid biopsy is a proven, minimally-invasive method to secure genomic insights, with the option to reflex to a tissue biopsy if ctDNA turns out to be insufficient to analyze."

"Both state-of-the-art tests and treatments, as well as new research, were presented virtually this year."

Two other studies examining genomic analysis of circulating cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) in advanced prostate cancer were also presented. In one of the studies, BRCA mutations were found in both liquid biopsies and in tissue; a comparison was made. The prevalence of BRCA1 mutations was much higher in the liquid biopsy specimens; the opposite was true with BRCA2 mutations. In the other study, genomic analyses were performed of 3,334 patients with advanced prostate cancer using ctDNA from the TRITON23 Trials and routine comprehensive genomic profiling. Dr. Hanna Tukachinsky of Foundation Medicine stated "…the majority of patients with advanced prostate cancer have abundant ctDNA that can be tested using comprehensive genomic profiling to support doctors as they consider targeted therapies for their patients…". She also said, "Although a large proportion of patients in this study had detection of BRCA alterations in both their tissue and liquid biopsies, some patients had no sign of BRCA alteration in their tissue biopsy taken years earlier, while having a high variant allele frequency of BRCA alteration in liquid. These patients could benefit from treatment with PARP inhibition."

Speaking of PARP inhibition, a gene-by-gene analysis of DNA repair mutations in patients with mCRPC in PROfound, a Phase III study, found that patients with BRCA alterations had the most important antitumor activity on olaparib. The study points out the importance of genetic testing for all patients with high-risk mCRPC and highlights the potential overall survival (OS) benefits of treatment based upon that testing. Genetic counseling is also advised. And in a randomized phase II trial reporting out of UC San Diego, investigators did a biomarker analysis of olaparib with or without cedirinib in men with metastatic castrate-resistant prostate cancer (mCRPC). Recently two PARP inhibitors have been approved in mCRPC for men who had certain gene alterations associated with homologous recombination deficiency: olaparib and Rucaparib. This study compared olaparib, with olaparib in combination with cediranib, an oral antagonist of VEGF receptors. There were a total of 90 patients, most of whom (unlike in PROfound) were heavily pretreated. One arm received the standard dose of Olaparib (300 mg twice a day) and the other arm received cediranib plus a reduced dose of olaparib. Crossover was permitted from the olaparib-only arm to the other combination arm at time of progression. The primary outcome was met: an improved radiographic progression-free survival (rPFS) in pretreated mCRPC, independent of homologous repair gene status, although the benefits appeared stronger in those patients with tumors deficient in homologous recombination.

The SAKK 09/10 randomized Phase III trial was also presented at the meeting, comparing a dose-intensified approach to salvage radiotherapy versus a conventional dose. The new study showed that the dose-intensification was not superior in patients with biochemically recurrent prostate cancer who had undergone a radical prostatectomy. 170 patients received 64 Gy and 174 received 70 Gy. The study did not meet its primary endpoint: freedom from biochemical progression. Additionally, there was no difference in progression-free survival or time to ADT.

The ACIS study was a randomized, placebo-controlled double-blind Phase III study of apalutamide and abiraterone plus prednisone (AAP) or abiraterone plus placebo and prednisone. In other words, 982 patients were randomized to receive abiraterone and prednisone with or without Apalutamide. Baseline characteristics were similar in both groups. The overall data showed that the trial met its primary endpoint of rPFS; this primary endpoint was met with benefit with AAP (a 30% reduction); however, after 54.8 months of median follow-up, although overall survival was numerically higher it was NOT statistically significant. Other secondary endpoints were also similar. It is interesting to note that more patients who also had apalutamide had at least a 50% decline in PSA levels, and in fact undetectable PSA levels at some point during their treatment. But the median time to PSA progression did not differ between the two groups. While there were no unexpected adverse events (AE's), those who received apalutamide had more fatigue, hypertension, skin rash and cardiac disorders. Questions remaining from the trial: whether apalutamide's androgen signaling inhibition means better outcomes for patients, and whether or not androgen inhibition after progression is helpful for those patients.

Final results of the Phase III TITAN study were presented, and demonstrated the continued statistically significant benefit of adding Erleada (apalutamide) to ADT in overall survival (OS) in patients with metastatic castration-sensitive prostate cancer (mCSPC), no matter the extent of disease, when compared to placebo plus ADT. Dr. Kim Chi, principal investigator of the TITAN Trial, stated, "The TITAN final analysis further confirms that treatment with apalutamide can prolong overall survival and offer a clear long-term clinical benefit and established safety profile for patients with metastatic prostate cancer who are starting androgen deprivation therapy. Based on these data, ADT alone should no longer be considered sufficient for patients with advanced, castration-sensitive disease."

Another interesting presentation from Dr. Felix Feng at UCSF discussed the Decipher Test as a guide to post-surgical therapy in prostate cancer. He showed that scores with the 22-gene Decipher Genomic Classified (GC) were independently associated with risk for metastasis, prostate cancer-specific mortality, and overall survival (OS) among patients with recurrent disease who were treated with salvage radiation therapy with or without bicalutamide. The results are important in that they mean that not all men with biochemically recurrent disease (BCR) after surgery will benefit from hormone therapy. This was also an ancillary study of the NRG/RTOG 9601 Randomized Clinical Trial and was published in JAMA Oncology online on February 11, 2021. The findings as described by Dr. Feng will likely help with shared decision-making between physician and patient. Dr. Feng noted that the findings of the study can be quickly incorporated into clinical practice. He stated the importance of personalizing all therapies for men with prostate cancer.

In a panel presentation, Dr. Michael Morris of Memorial Sloan-Kettering Cancer Center asked about patients with low-risk disease but BRCA pathogenic mutations. Should there be prophylactic strategies for treatment? And who should be referred for genetic testing? He concluded, to answer that: Yes, for patients with a personal history of high-risk disease or metastases; and/or patients with a family or personal history of cancer (eg, associated with either BRCA1 or 2, Lynch Syndrome or HOXb 13 positive). He might suggest tumor-only sequencing with BRCA1 or 2 or other mutations. He referenced the NCCN Hereditary Cancer guidelines and nonprostate cancer risks and screening for BRCA1 and 2 positive men. Dr. Morris stated that about 17% of men with localized disease have germline mutations predisposing them to

prostate cancer. His work that was presented was also pubished in JAMA Oncology that day. Dr. Morris stated that the median survival time is five years in carriers, and 16 in non-carriers, showing the aggressivity of the BRCA mutation. He then referenced the study in European Oncology which showed that positive BRCA status is about 3 times the increased risk of metastases and prostate cancer-specific mortality than non-carriers, but that 75% of men with BRCA1 or 2 germline mutations will not be diagnosed with prostate cancer. There was also discussion of monoallelic loss versus biallelic loss. Lastly, Dr. Morris stated that there is no indication that BRCA-mutated tumors are more radio-sensitive.

A "Real-World Evidence Study" presented by Dr. Stephen Freedland looked at how men in the Veterans Health Administration have received treatment over the past 15 years, given all of the developments in prostate care during that time. The investigators identified patients with metastatic castration-sensitive prostate cancer who had ADT alone or ADT with anti-androgen, docetaxel, or abiraterone between April 1, 2014, and March 31, 2018. Their data obtained showed that most patients with mCRPC in the VA System were treated with ADT only, even though there is Level 1 evidence supporting the use of docetaxel and Novel Hormonal Therapies (NHT's).

In a retrospective study out of France, researchers queried whether OS in mCRPC could be improved with multiple cabazitaxel rechallenges. Currently cabazitaxel is typically utilized in the second-line chemotherapy setting. A presentation in the Poster Highlights Section at ASCO GU looked at the feasibility and efficaciousness of multiple cabazitaxel challenges in these mCRPC patients. The conclusion of these investigators was that repeated rechallenges with cabazitaxel may extend OS without unmanageable toxicities.

In metastatic castration-resistant prostate cancer (mCRPC), a study out of the University of Michigan showed that a new oral docetaxel formulation known as ModraDoc006, when combined with ritonavir, had definite advantages over IV chemotherapy for these patients – it was convenient, taken by mouth, and better-tolerated. ModraDoc006 was given twice a day (20 mg and 200 mg of ritonavir) along with 5 mg of oral prednisone. Another benefit of oral administration was seen because of the pandemic. Use of the oral agent avoided the risk of infection from cytopenias and neuropathy, frequently seen with IV docetaxel. The primary endpoint of the study was radiographic progression-free survival (using criteria from the Prostate Cancer Working Group 3). Study investigators are optimistic about the drug development of this agent, which had "a favorable toxicity profile and comparable efficacy."

Poster Sessions also had some interesting reports and findings. For example, Genomic Health Incorporated (Exact Sciences) posited that "Adverse pathology at radical prostatectomy is highly associated with future development of metastasis and prostate cancer mortality and may be used as a short-term predictor of outcomes."

UCLA presented a poster on the "Association of reductions in PSA screening across states with increased metastatic prostate cancer" and concluded: reductions in PSA screening may explain some of the recent increase in metastatic prostate cancer at diagnosis in the United States... a worrisome consequence that needs attention…we support shared decision-making policies, such as the 2018 USPSTF update, that may optimize PSA screening utilization to reduce the incidence of metastatic prostate cancer in the United States." ….Another poster reported on a group that evaluated the prevalence of homologous recombination repair gene (BRCA 1/2 and ATM) mutations (HRRm) in a real-world prostate cancer population that had commercially available cfDNA assay results available. The poster postulated that there is a rationale for utilizing cfDNA comprehensive genomic profiling as a routine test for detection of HRRm to identify those who are appropriate candidates for PARP Inhibition.

Another significant poster presentation was submitted by Johns Hopkins, looking at cell cycle progression score and PTEN as prognostic factors for metastasis in intermediate- and high-risk prostate cancer overall. These had never been evaluated together as prognostic markers for risk of metastasis in a radical prostatectomy cohort of men with NCCN intermediate- or high-risk prostate cancer, nor in those patients who also received salvage radiation therapy alone or with androgen deprivation. Conclusion: CCP score, but not PTEN, was significantly associated with metastasis-free survival. Myriad Genetics participated.

Other Poster Sessions: "Adverse pathology at radical prostatectomy is highly associated with future development of metastasis and prostate cancer mortality and may be used as a short-term predictor of outcomes." (Genomic Health, an Exact Sciences corporation)

Lastly, there were a few posters on the use of darolutamide (DARO). One examined the safety of darolutamide for non-metastatic castrate-resistant prostate cancer (nmCRPC) as an extended follow-up to the ARAMIS Trial. Darolutamide remained well-tolerated. And looking at the effect of crossover from placebo to darolutamide on overall survival (OS) in the ARAMIS Trial, the conclusion was, "Early treatment with DARO in men with nmCRPC is associated with significant improvement in OS regardless of pts crossing over from PBO to DARO. The safety profile of DARO remained favorable at the final analysis."

Although ASCO GU 2021 was a virtual, not an in-person meeting this year, attendees received an abundance of excellent scientific results in prostate cancer, learned about interesting trial results, heard from superb speakers, and were encouraged about the future of targeted therapy in prostate cancer.

Next year in person in San Francisco at ASCO GU 2022! Pp

Jonathan Epstein, MD
Pathology + Prostate Cancer

Dr. Jonathan Epstein, of The Urologic Pathology Laboratory at Johns Hopkins University Hospital, is a leading authority in urological pathology of prostatic and bladder disease. He is the author of over 800 articles, as well as the definitive texts, *Prostate Biopsy Interpretation* and *Bladder Biopsy Interpretation*.

Dr. Epstein consults frequently with pathologists, physicians, and patients.

Prostatepedia spoke with him recently about the role of the pathologist in prostate cancer, Gleason Grades, and testing for prostate cancer.

What's the role of the pathologist in diagnosing prostate cancer?

Dr. Jonathan Epstein: There are several roles. First, is an accurate diagnosis of cancer versus not cancer. Which to somebody who's not an expert in the field, or not a pathologist, might seem obvious. But, actually, the diagnosis of prostate cancer is one of the most difficult diagnoses in all of medicine, compared to other organs, and can often be underdiagnosed or overdiagnosed. In addition to getting the correct diagnosis of cancer, the second most important factor is accurate grading, which determines prognosis and treatment. Which, again, is not straightforward. In probably 20% of the cases sent to me, I changed the grade significantly.

20%?

Dr. Epstein: Right. The third role of the pathologist is to quantify the cancer, which can be less important than grade but is still one of the factors that goes into treatment and prognosis.

> *"The diagnosis of prostate cancer is one of the most difficult diagnoses in all of medicine."*

What's the importance of experience in recognizing these patterns when you're analyzing the tissue?

Dr. Epstein: Experience, education, and training. When I was in the field early in my career, there were no fellowships subspecialty training for urological pathology, which includes prostate cancer diagnosing. So I learned it on my own and became an expert on my own. Nowadays, there are fellowships and we have the largest one in the world. We have four to five people a year who are trained and then they go out, and some of them eventually become leaders in their field.

There's also an art to pathology, as well as a science. Meaning there are some people who can have all the experience in the world, but they'll never be great pathologists because they just don't have what we call an eye for pathology. There is something, just like a painter or a photographer has, a skill and vision in putting together patterns and recognition. It's the same with pathologists. Part of it is the science and part of it is, somewhat, the art.

Last time we spoke, you'd just come out with the new Gleason grading system. I want to return to that, but first, could you give a brief rundown of the differences between this newer one-to-five system and the older system that most men are familiar with?

Dr. Epstein: The motivation for coming up with a new, simpler one-through-five rating system for prostate cancer was the old system theoretically goes from two, the lowest grade, to 10, the highest grade, but it has evolved such that six is actually the lowest rate that anyone is assigned. So we have a grading system, using the Gleason system, which was devised in the 1960s and '70s, that starts with a six as its lowest grade. Anywhere else in the body, you don't start with six. Intuitively, it makes no sense to start with six being the lowest. The lowest grade for all other tumors is always one.

Patients are potentially confused when they're given a six, yet they're told, "This is as low as you can get." That was one reason for coming up with a new grading system. The other is the Gleason seven, which sounds like just one number, but there are actually two different grades you can have with a Gleason seven, either 3 + 4, where there's a predominance of the lowest pattern three. Or 4 + 3, where there's a predominance of a pattern 4, with a lesser amount of the 3. And they're very different in prognosis, extremely different. But are lumped together as 7.

In the new grading system, they are cleanly separated out as Grade 2 and Grade 3; you just can't combine them. On a similar line, clinicians and the literature would lump 8, 9, and 10 together as monolithic high-grade prostate cancer, where 8 has twice as good a prognosis as 9 and 10. There are different treatments. In the new grading system, 8 is a Grade Group 4, 10 is a Grade Group 5. You can't combine them.

What has the process of adoption been like and where do you see this newer system now in the context of the prostate cancer treatment?

Dr. Epstein: Adoption has been widespread. It is still used in conjunction with the old grade. For example, 3 + 3 = 6 is Grade Group 1, or 3 + 4 = 7 is grade group 2. It hasn't evolved to the point that it's replaced the Gleason system, but things take a long time to evolve. I'm pleased that it's been as widely adopted as it has.

It's so much more intuitive.

Dr. Epstein: Right. It's just a simple system.

I guess it's going to take time for people to get used to the new way of thinking.

Dr. Epstein: All the current trainees will be familiar with it and be comfortable with it. Hopefully, with their generation and the subsequent generation, it'll be, "Why have we been using this older system?"

Are there any particular tests for prostate cancer that you recommend?

Dr. Epstein: There are several different tests. I would say some are controversial. There are various molecular tests that are, for the most part, commercially driven and proprietary in terms of what genetic testing they're doing. These were mostly developed on radical prostatectomy specimens to predict prognosis. The assumption is we can apply it to needle biopsies where it's more critical in terms of treatment and prognostic decisions to help patients. For example, to decide if they stay on active surveillance or not.

However, there have not been significant, large, long-term follow-up studies using those molecular tests on patients, for example, with active surveillance to say, "Do they truly predict who's going to do well or not?"

Anecdotally, I know of cases, one just recently, a patient was totally confused because they had an aggressive prostate cancer based on grade and, by all accounts, that patient needed aggressive treatment. It was a Gleason 8, Grade Group 4. And their molecular tests came back saying, "This was a good prognosis. You're an excellent candidate for active surveillance." No urologist in the world would put that patient on active surveillance, and, obviously, it confused the patient to no end.

I'm not a big proponent of these molecular tests. I think the major problem that we still have with prostate cancer is sampling. You see it all the time where somebody has a Grade Group 1 everywhere and a small amount of Grade Group 5 in one corner—a Gleason 9 or 10 cancer that could have easily been missed. Or, similarly, somebody who has a small amount of Grade Group 1, a Gleason 6, last year. And then they get a repeat biopsy this year and there's high-grade cancer. It's not that the high-grade cancer evolved in one year, it was missed.

The problem with these tests is they propose that they can identify a low-grade cancer that is truly not low grade, that it's really a bad cancer, even though it looks low grade under the microscope. I'm not convinced, and I don't think their studies are convincing along that line. I think ultimately if you miss the high-grade cancer, those molecular tests aren't going to help you.

I think the money is more on multiparametric MRI and enhanced sampling, finding the aggressive cancers, as opposed to testing on

the low-grade cancers. We do a test at Johns Hopkins for one molecular marker. It's not a commercial antibody. We test for PTEN loss in low-grade prostate cancers, which only occurs about 5% of the time.

There is data to suggest that loss of PTEN is associated with more aggressive tumors. Again, maybe these are the aggressive, low-grade cancers that you want to treat, and not put on active surveillance. That's still an area that's more of a researcher endeavor; it's not something that's uniformly done. I'd say it needs additional data.

There's also testing that we do for, on the opposite end of the spectrum, patients with very high-grade prostate cancers, looking for a loss of microsatellite instability, which can determine whether patients could benefit from certain therapies. Other tests look for certain mutations where patients may have a genetic predisposition for high-grade prostate cancer that could have implications for family members and other types of tumors. So that testing is also being done, in some cases for treatment, and in others for genetic counseling. Most of this testing is being done in-house more and more. It used to be that those were all things that were sent out, but now most academic centers are doing them in-house.

Do you think it behooves the patient to ask his doctor about some of these tests?

Dr. Epstein: Yes, I think it's reasonable. I think it's great for patients to get as involved as they want and as much as they feel they can be in their own care. I think the more they know about their disease and the more they get involved, the less likely it is something might fall through the cracks. I also think it's more likely that they will get the best choices for therapy and ultimately the best treatment.

It's up to patients to understand the chart and understand the report. If they don't understand it, ask questions. It's one of the things I get all the time. I talk to two or three patients a day, which is unique amongst pathologists. One of the things almost all of them do is thank me for spending so much time talking to them because sometimes they just don't get all the answers they need from others.

Talk to me about how you talk to patients. It was my understanding that usually the tests or the pathologist report is ordered by the oncologist or the urologist and it gets sent directly to them and you're not really in contact with patients. Are these people seeking second opinions from you?

Dr. Epstein: I'm relatively unique in that. I get about 35 prostate cases a day and probably 15 to 20% are patient-driven, where the patient has found me either on the Internet or webinars. I'm also listed in various lay-books, written by experts in the field. I am also mentioned in various prostate cancer support groups.

I think it's important to get second opinions. Patients take it upon themselves to get their cases sent to me and a subset of those want to talk to me about the report. Many don't. They're content to get the report and see if it matches with the original and go from there. However, a the subset wants to talk to me and I gladly do so.

So it's your role as a key opinion leader/subject matter expert that makes these people reach out?

Dr. Epstein: Right, and I don't treat patients. I'm not a urologist. I'm not a clinician, but I know enough about the disease and the treatments that I can offer them advice. Ultimately, they have to speak to their clinicians because I don't know all the medical conditions, et cetera, but I can inform them to a great extent.

> *"There have not been significant, large, long-term follow-up studies using those molecular tests on patients."*

Any further comments for men with prostate cancer?

Dr. Epstein: Just that they should take ownership. The first step is to recognize that there is a pathologist coming up with the diagnosis, not their clinicians, even though they don't know the pathologist. The other thing I would emphasize is most pathologists, the vast majority, are very good and very competent. So I'm not casting aspersions on Pathology as a whole or about pathologists relative to prostate cancer. But there's a subset of pathologists who are not as adept at prostate cancer pathology because it is very difficult, either because of lack of training, experience, or they just don't have that eye for pathology. And as the patient, you don't know who your pathologist is. It could be a good institution but still the pathologist may not have great expertise in prostate cancer pathology.

Just two days ago, and I won't name the institution for obvious reasons, a patient was diagnosed with a very favorable grade prostate cancer. He thought he could go on active surveillance, a very limited treatment. The diagnosis was from a top institution and he trusted that institution. The institution is excellent overall. It turns out that the grade was overtly wrong, and he actually has very aggressive prostate cancer that needs entirely different treatment. Had he not sought out a second opinion, he would have been undertreated and the cancer would have ultimately, almost undoubtedly, killed him. Because he took the initiative, he will be treated correctly.

You can't just rely on what institution it is or how good your doctor is because the pathologist can be extremely variable and behind the scenes. Everything is ultimately going to be driven by the pathologist: your prognosis and your treatment. It behooves you to get a second opinion. Once you get the second opinion, you trust it, and you're on the right track for the rest of your treatment.

How would you recommend patients find someone for a second opinion? How do you identify your second-opinion pathologist?

Dr. Epstein: You can go through support groups, you can check on the Internet, or you can ask your urologist who they would recommend. They typically know who the experts are. You can see who's written the books about it. There are multiple different ways to go about it. Pp

Jeffrey Ross, MD
Genomic Profiling

Dr. Jeffrey Ross, Medical Director of Foundation Medicine, is a leader in the field of molecular diagnostics, having received a number of academic awards, been awarded three patents, and authored more than 600 peer-reviewed scientific articles and abstracts, four textbooks, and numerous book chapters in the fields of pathology, molecular diagnostics, oncology, and translational cancer research.

Dr. Ross is the Jones-Rohner Endowed Professor of Pathology and Urology at the Upstate Medical University in Syracuse, NY, where he directs the Molecular Tumor Board Program.

Dr. Ross spoke *Prostatepedia* about genomic profiling for prostate cancer.

Understanding genomic versus genetic testing can be confusing for patients. Can you explain the difference?

Dr. Ross: Although I'm a pathologist, I see both breast and prostate cancer patients in my academic practice. I review with my patients some of the more sophisticated molecular diagnostic tests they had done in their disease and help explain to them the impact it has on their plan for therapy. It's more about the implications of the tests for the patients rather than the tests themselves.

I personally like to use the word "genomic" to refer to a group of DNA- or RNA-based assessments of a patient's disease, rather than one single assessment. It's testing their disease specimen, looking for biomarkers, or predictive results, that will help them get an individualized treatment regimen rather than a one-size-fits-all approach.

"We don't care so much where the cancer started."

Genetic testing, or genetic-based testing, I've always restricted to looking at the patient's germline. It looks to the DNA they inherited from their mother and father that can, in some cases, make them susceptible for the development of cancer or, as we know now, also predict their responsiveness to certain types of anticancer drugs, classic being the BRCA1 and 2 genetic, rather than genomic, predispositions for cancer. This germline test will also now predict that they could benefit from a class of anticancer drugs called the PARP inhibitors.

So, they both have a role?

Dr. Ross: They are absolutely deeply connected, running in parallel. There are some types of cancer in which germline genetic testing is done on almost every patient. Prostate cancer is moving strongly in that direction. There is so much of the disease that does occur on a predisposition basis, not just randomly, but because they inherited a risk for it from either their mother or their father, that many urologic oncologists want germline genetic testing on all their prostate cancer patients, especially young patients. So, they could be even in their 40s but particularly when they're in their 50s and 60s. They want genetic testing to make sure it's not a family basis for the disease because that could have implications for the man's family members, as well as, for the treatment that the man may ultimately undergo.

Do you think genetic testing should be done on the families of men with prostate cancer?

Dr. Ross: It depends on a lot of clinical background. Firstly, is this the first man in the family ever to develop prostate cancer that anyone knows about? In addition, there are specific recommendations for germline genetic testing for African American men for whom prostate cancer is a major health risk. And is this man relatively senior, perhaps past the age of 60, 65, or 70? Then I would say, no.

On the other hand, is this a younger man who especially presents with biologically aggressive disease, a high Gleason score, or multiple core biopsies positive? Extensive disease presenting in a young man usually triggers an extensive evaluation of the man's family history, often taken by a genetic counselor, followed by a decision whether to do germline testing or not. So, you wouldn't do it on everyone. Remember, this disease is incredibly common and incredibly benign in the majority of patients. In the life-threatening cancer group, prostate cancer is one of the most benign that we know because the vast majority of patients who have it diagnosed during their lifetime will either be cured of the disease or will not die from living with it.

Unfortunately, prostate cancer is so common that those who are not going to be cured by primary treatment do not represent just a few hundred patients here and there, they represent thousands of patients. And that's been testing's ongoing dilemma since the beginning, which was only made even worse in the early 1990s with the introduction of widespread PSA screening.

Between 1989 and 1991, we diagnosed maybe 120,000 to 130,000 new cases of prostate cancer. Within a period of two to three years, that number rose to about 380,000 new cases a year. All of those men who were living happily with prostate cancer, were maybe never going to know they had it, and were never going to die from it, went for the PSA test and they got diagnosed with the patients who hadn't been diagnosed the year before that and the year before that.

We then had this huge cohort. As we went into the mid and late 90s, it fell back to the 200,000 to 220,000 new cases a year in the US that we see now. But remember, with PSA screening then, everyone thought you were saving a man from the risk of dying from prostate cancer, not understanding that you were saving only a percentage of those men from the risk of dying of prostate cancer. While at the same time, potentially ruining the lives of all of the other men who were never going to die of the disease and, now, could become incontinent or impotent or have some other serious complications from primary therapy, either by surgery or radiation.

This is why it's essential to be able to differentiate which man has aggressive prostate cancer and which has cancer that will just be indolent.

Dr. Ross: We've been working on that for about 35 years.

What's the difference between biomarker testing, genomic profiling, and tumor profiling, or are these the same things?

Dr. Ross: They all have something in common, for sure. Biomarker is a very broad term. (This is coming from now my second year of medical student lectures on this topic.) Here are some examples. You're losing weight and you can't explain it and then you're diagnosed with cancer, well, weight loss was a biomarker for your cancer. You've got a fever and then you've been diagnosed with an infection, well, fever was a biomarker for your infection. It's a very broad term.

But in cancer, we tend to use the term biomarker to mean something that was obtained from the patient — a blood sample or a tumor biopsy — that has been analyzed by some laboratory test and that has an impact on the patient's disease. That impact may be its diagnosis, predicting its prognosis, scheduling its therapy, or predicting response to therapy. Those are all biomarkers.

Cancer genomics—which is what we do at Foundation Medicine—is trying to find out what are the cancers' Achilles heels. What are their vulnerabilities to the therapies we currently have? How can we match that patient with advanced disease to a clinical trial of other patients that have the same biomarker? Or that they've done the genetic-based testing of the germline to predict another family member's risk of developing it. That's a biomarker. So, they're all overlapping.

Genomic tests overlap as biomarkers, genetic tests overlap as biomarkers, and, certainly, the serum PSA test is a biomarker. It's a really good biomarker to monitor the course of the disease, predict the patient's likelihood of being cured, the likelihood of being at risk for relapse, and responding or not responding. It's really good. The serum PSA test is not as good a screening test for who does and who doesn't have disease we need to treat. It will detect all disease,

but it won't easily separate disease we need to treat from disease we don't need to treat. But it's still a biomarker.

And tumor profiling?

Dr. Ross: Tumor profiling is certainly a biomarker but, in this case, the patient already has the diagnosis of cancer, so this is not a diagnostic test to establish the presence of the disease. Genomic profiling, in general, is not a prognostic test because if the patient had good-prognosis disease, they never would have had the test ordered in the first place, meaning they were cured by their primary treatment. Their PSA was elevated, they had a biopsy, it was positive, the surgeon did a radical robotic prostatectomy, and now the PSA is unmeasurable. PSA is doing a great job as a biomarker there and the patient doesn't need profiling because there's no more cancer left. So, prognosis is not, for the most part, what profiling does.

Profiling is designed for the at-risk patient—the clinically advanced disease patient—to try to match the biology (the genomic profile) of their tumor to some therapy that has a better chance of taking that rising serum PSA and reducing it back to zero, rather than just any therapy that's used for all patients, regardless of whether they had genomic testing or not. It's personalizing the treatment.

What specific genomic tests is a man with prostate cancer likely to encounter along the journey?

Dr. Ross: I'm mostly focused on genomic profiling for therapy selection. The vast majority is done on metastatic castrate-resistant prostate cancer (mCRPC). We do receive, very uncommonly, samples to profile on patients who have hormone-sensitive disease, which means their PSA is under control and they are still on some type of hormonal ablation treatment. I mostly restrict my comments to men who have progressed beyond hormonal therapy. This is what Foundation Medicine sees 97 to 98% of the time, a castrate-resistant prostate cancer sample.

Sometimes, we run into trouble when using genomic profiling to select precise therapy because, although the man clearly has that, his PSA is going up, his imaging is showing new lesions, new bone involvement, and new visceral organ involvement, but the sample that's sent to Foundation Medicine is the original needle biopsy of the prostate cancer taken months or even years before any hormonal or other therapy had been given. That specimen unfortunately is just not that useful. We need post-treatment samples to help guide new therapy selection. That can come from a metastasis biopsy or a blood-based liquid biopsy such as FoundationOne Liquid CDx.

And I'm assuming prior therapy can change the cancer, right?

Dr. Ross: Exactly. We need a contemporary biopsy of a metastatic site, which is particularly a problem if the patient has bone-only metastatic disease. Unfortunately, with a lot of men with metastatic prostate cancer, the only evidence of the metastatic disease is widespread in his bones. Those are not good samples for sequencing because the bone gets in the way of getting the DNA safely out, so we have to decalcify it, remove the calcium from it in some way, which damages the DNA and can interfere with the actual sequencing test. Genomic testing for prostate cancer does not like to do it on bone metastasis biopsies and that's why the blood-based test, the so-called liquid biopsy, or in our case, FoundationOne Liquid CDx, has been increasing rapidly in popularity among medical oncologists who have now taken over the patient's treatment.

Once CRPC develops, the urologist has referred the patient to the medical oncologist.

During the hormone-sensitive therapy phase, the urologist is still significantly involved but once the PSA starts going up despite hormone ablation regimens, the patient starts getting new symptoms, and radiology possibly including an-anti-PSMA scan shows new tumor sites or growing tumor sites, then the medical oncologist essentially takes over. What's become a more and more important issue is when should the profiling have been done and what sample should it have been done on?

I personally believe that genomic profiling is being delayed too long for many prostate cancer patients. Most men with advanced prostate cancer are being considered one-size-fits-all, not only through the conventional hormonal therapy, but also into the next phase of treatment called novel hormonal therapy with new hormonal therapy agents. And then, when disease progression occurs after all hormonal therapy we have CRPC and treatment moves to cytotoxic drugs, usually with docetaxel, and then if there is still further disease progression, genomic profiling is ordered for the first time.

I believe genomic profiling in prostate cancer should be done much earlier, maybe even before hormonal therapy because there are some biomarkers that can be discovered by the profiling that could lead a man to avoid hormonal therapy entirely and select other treatment plans. Hormonal therapy is life-changing. Quality of life can often be seriously impacted.

Profiling before hormonal therapy may reveal a target, known as the BRCA2 deletion, which can be treated with the PARP inhibitors and achieve dramatic and long-lasting results. This is different from BRCA1 and 2 gene sequence mutations which more quickly develop resistance mutations that limit the PARP inhibitor benefit.

Why wouldn't you do genomic testing of that initial biopsy prior to a diagnosis of cancer? Is it just a cost logistics issue?

Dr. Ross: A needle biopsy is the gold standard. The pathologist looks under the microscope at the needle biopsy of the prostate. Sometimes the man will present with metastatic disease and you get a stage-four metastatic site sample like a liver biopsy as the first sample but that's very rare for prostate cancer. The surgical pathologist makes the diagnosis, determining the risk of the presence and the development of advanced disease based upon how many biopsies are positive, what percent of the core is positive, the primary Gleason grading pattern, the secondary pattern, and the total score. All of this will be added together with the height of the patient's PSA level, the rectal exam findings, and maybe MRI of the pelvis.

And then, the urologist meets with the patient and says, "You have really indolent disease, only one core positive, Gleason 6. I'm not worried at all. We'll just check your PSA in six months and make sure it's

not going up too fast. Have a nice day." That's watchful waiting.

Which is what you want.

Dr. Ross: That's what you want. Or you'll see too many cores involved, you'll see maybe pattern 8 even beyond 7, which is extremely worrisome.

The patient will be told, "You need serious primary treatment, either a robotic radical prostatectomy or the combination of external beam and intratumoral seed implantations of radiation, both of which can cause serious side-effects including impotence, incontinence, and other adverse events. But if you don't do that, I'm very concerned you will die of this disease and die fairly soon and miss out on a lot of good years you have left."

The man will say, "I want surgery. I want to get it done in one day." Another man will say, "I don't want to have surgery. I'm happy to go for radiation for weeks, even though it takes longer, I don't have to be admitted to the hospital, ever."

Can you envision a time in the near future when we do genomic profiling on all patients who fall into that second scenario you described?

Dr. Ross: There are many, many companies, you must have heard of Genomic Health and the Oncotype DX test for breast cancer. They've tried to extend Oncotype DX into prostate cancer in the same way, but it just hasn't been widely adopted. There are urologists who are confident it can help decide who to operate on but many urologists are not using this test at the current time. The Oncotype DX for breast cancer works so well because it helps decide whether or not they should have chemotherapy in addition to hormonal therapy or just hormonal therapy alone. And that's a very different question than, should we radiate or should we operate on a man with prostate cancer.

There are many other tests and diagnostics companies working in this space, it's a critically important issue, maybe one of the top medical dilemmas in cancer that still exists today, just like it did 35 years ago: who to treat vigorously and who to not treat vigorously.

We're getting better at it but we're far from hitting the bulls-eye when we treat every man who needs it and when we let every man whowe don't need to treat go and have a nice day.

What about companion diagnostics that go along with these?

Dr. Ross: Not all of the results we find doing genomic profiling have become companion diagnostics. Prostate cancer is quite a bit behind lung cancer, or even breast cancer, in this regard with these tumors already having multiple companion diagnostics already approved by the FDA. Foundation Medicine is working with the pharmaceutical oncology industries to try to find more companion diagnostics for novel drugs including those planned for the treatment of metastatic CRPC.

Right now, for metastatic CRPC, the only companion diagnostic that is FDA approved is for the selection of PARP inhibitors, for the BRCA1 and 2 mutations and then another gene called ATM. These genes are involved in DNA damage repair and, when identified, can cause HRD deficiency. That means the patient's DNA breaks easily which renders them sensitive to these PARP inhibitor drugs. Other companion diagnostics are in development for metastatic CRPC patients but have not been approved by the FDA to date.

We are hoping that will change over over the next several years.

Are most of these tests covered by insurance?

Dr. Ross: Yes, they are. PSA tests are covered and that's not a problem. When it comes to genomic profiling, a large portion of men with prostate cancer are Medicare beneficiaries and the FoundationOne CDx test and the FoundationOne Liquid CDx test are approved by the FDA and, thus, are allowed for reimbursement by Medicare.

Getting the test paid for isn't usually an issue for the average patient?

Dr. Ross: Not prostate cancer, no because of the patient's age and being under Medicare. Not all insurance companies will reimburse, but most do because these are elderly patients at great risk of harm from their disease, so they don't usually oppose covering the cost of the profiling test.

On occasion, if you want to do a second profiling test on the same patient, you can get some pushback by the payor and you have to validate the medical necessity for that. That can be difficult. It usually will be successful, but it's not automatic. Once the patient's insurance has paid once for genomic profiling, it may require a lot of negotiation for them to pay a second time.

Has the pandemic impacted the world of genomic testing? Have you seen patients choose to delay testing because of fears of the pandemic?

Dr. Ross: It has not. There is certainly a lot of medical care that's been impacted by COVID-19, but not as much for patients living with established cancers.

Where the impact in cancer care is greatest, I think, is in delay of diagnosis: Patients with symptoms not coming in to be evaluated and adding weeks or months for their cancer to progress beyond a point we can cure them or even palliate them well.

For patients whose cancers have already been diagnosed and are known, the sending of the sample to Foundation Medicine for testing and sending the results back to the oncologist, all being done in the outpatient setting, has not been impacted by COVID. The volumes at Foundation Medicine reflect that there was not any decline because of COVID-19. It's not like delaying an elective surgical operation as it is almost entirely done in the outpatient/physician's office setting.

And for many patients, the sample that's needed to do the test already exists in a hospital pathology department archives and all that's needed is to alert them to take a portion of it and send it to Foundation Medicine. So no, not a big impact for this part of cancer care.

Do you think, down the line, that we'll see men diagnosed with more advanced disease because of these delays in diagnosis?

Dr. Ross: I think so. Hopefully, it will be a very small and short-lived blip but I think that'll happen. I think you'll see in all kinds of cancers, including prostate cancer, a greater frequency of advanced-stage disease at time of diagnosis than we saw before COVID. But, hopefully, this will only last for a short time.

What about the larger world of pathology? Have there been any changes in how you function during the pandemic?

Dr. Ross: Well, 99% of the other pathologists would say I'm not a good person to talk to about this because I've been a leader of doing things that have the potential to decrease the number of cancer-related samples that pathologists evaluate under their microscopes and the additional testing they do on those samples. Meaning that, for example, 5 to 10% of the cancers that come into Foundation Medicine have an unknown primary site; they couldn't find where it started. It's spread into multiple places and the pathologists locally have looked at it and done some tests and they're not sure and the radiologists aren't sure.

I've greatly advocated that we don't care so much where the cancer started at this point, assuming the patient can't be cured by a surgeon. Whether it started in the GI tract or the genitourinary tract or the breast or lung, unfortunately, now it's too late for an outright cure. What we can do at Foundation Medicine is find out using genomic profiling what's driving their tumor, what's making it grow, what's making it progress, and see whether those genomic drivers have drugs on the market or available through clinical trials that can be matched to their cancer cells that will hopefully cause them to regress or even disappear.

Thus, for these cancers of unknown primary site patients, both men and women, profiling for therapy selection is more important than finding where the cancer actually started. Also, I've been part of what are known as Pan-Cancer FDA approvals. Pan-Cancers drug approvals are directed towards "histology agnostic" cancers. For treatment selection, the pathologist diagnosis is less important if the genomic profiling shows the drug target is present. If they have a neurotrophic tyrosine receptor kinase (NTRK) fusion-driven cancer, no matter where it is, in the lung, liver, bone, soft tissue, genitourinary, gynecologic, anti-NTRK is the selected targeted therapy.

Research pathologists continue to ask, "What else can we learn from the microscopic slide beyond the traditional diagnosis that can help the patient get on a specific therapy? There's a lot of new evidence that digital pathology can expand the field of "predictive morphology." With the use of artificial intelligence of digitized pathology slide images, we may be able to achieve more treatment selection information from the pathologist than we currently provide when we just use the microscope to establish the diagnosis of cancer.

Any final thoughts for men reading this?

Dr. Ross: We want to help men with this disease everywhere we can. Sometimes it's trying to keep men from getting overtreated; that's also our job. But also Foundation's focus is to help the men whose disease is threatening their lives to help them live longer and better and be present at more graduations, more weddings, and important family moments. Pp!

Scott Tomlins, MD
Genomic Versus Genetic Testing

Dr. Scott Tomlins is Co-Founder, Chief Medical Officer, and Laboratory Director of Strata Oncology where he oversees precision medicine operations. He is an expert in the molecular pathology of cancer and precision oncology. Before joining Strata, he was an Associate Professor of Pathology and Urology at the University of Michigan Medical School, and he maintains an Adjunct position at the University of Michigan. Dr. Tomlins holds an MD and PhD from the University of Michigan.

He spoke to *Prostatepedia* about genomic profiling and its implications for prostate cancer.

What is the difference between genetics and genomic profiling? Why is it important to talk about them in the context of prostate cancer?

Dr. Scott Tomlins: A lot of these terms are not used precisely, so one of the most important things clinicians and testing companies can do in this space, particularly for prostate cancer, is to try to use precise terminology and language.

When I talk about genetic testing, I'm referring to tests to see if a patient has an alteration that is heritable, meaning they could have inherited it from their parents or could pass on to their children. Heritability can be tested for from basically any cell of the body. You can do a cheek swab or you could spit to collect cells from inside the lining of your mouth. You could use those to look for genetic changes, meaning DNA changes that are present in every cell in your body. You could also use a blood draw, where you take white blood cells and isolate DNA from those.

These genetic changes are present in the DNA of every cell in your body. They were either inherited or they are heritable, meaning they can be passed on. So that's what genetic testing is. The reason it's relevant in prostate cancer is there are a number of genes where a certain genetic change can put the man at a higher risk of developing prostate cancer over his lifetime. Some of these changes mean that they're more at risk for developing more aggressive prostate cancer, while some changes increase risk for early onset prostate cancer, meaning that they are at a higher risk for developing prostate cancer at a younger age than men that don't have those genetic changes.

Many of the most relevant genetic changes for prostate cancer occur in genes related to DNA damage repair. All the cells in your body are constantly exposed to substances that can damage DNA. These could be external things such as sunlight or internal things such as free radicals or infections. Your cells have evolved many ways to repair DNA damage. Genetic defects in the genes that repair DNA damage can predispose someone to developing cancer in general. Defects in several DNA damage repair genes can predispose to prostate cancer, most commonly genes involved in homologous combination DNA damage repair genes, including BRCA2, BRCA1, and ATM. These are abbreviations for genes that have long names, but that's what they're referred to, and collectively defects in these genes are often referred to as HRD (homologous recombination deficiency).

A lot of people, particularly women, are familiar with BRCA, which is commonly thought of as a breast cancer gene. BRCA is really two genes: BRCA1 and BRCA2. There has been a lot of effort in the breast and ovarian cancer communities to say, "Let's make sure we're doing genetic testing for BRCA because that can predispose to early onset ovarian or breast cancer."

Genetic changes in BRCA2, in particular, can predispose to prostate cancer. That's one of the main reasons that genetic testing is relevant in prostate cancer, to find these genetic changes that are associated with HRD. If a man finds out that he's a carrier of one of those genetic changes that predisposes him to prostate cancer, that's relevant for his relatives including children, whether they're men or women. It could explain a cancer family history from either the maternal or the paternal side. It may have implications for deciding if that man's children should be tested to see if they have the same change, even if they haven't been diagnosed with a cancer yet. Men with such genetic changes may choose to undergo more intensive screening for prostate and other cancers.

To put the frequency of these genetic changes in perspective, if you take a largely Caucasian population, of all men that have metastatic cancer, anywhere from 5% to 15% may have a genetic change in one of these DNA repair genes that may predispose to prostate cancer. They are less frequent in men with less aggressive cancer. Because of this high relative frequency, there are guideline recommendations from the National Comprehensive Cancer Network (NCCN) saying that any man who's diagnosed with metastatic prostate cancer should get genetic testing for these DNA repair genes, most importantly BRCA2, BRCA1, and ATM. They also recommend testing for genes that are involved in another kind of DNA repair pathway called mismatch repair (MMR). If genetic changes are present, this leads to deficiency in mismatch repair (dMMR). These are genes that more commonly predispose to early onset colorectal, or endometrial cancer, and most commonly include MSH2, MSH6, MLH1, and PMS2. Genetic changes in these genes can rarely also predispose to prostate cancer. Most of these guideline groups recommend genetic testing for all men who have metastatic disease and a subset of men who present with aggressive disease.

What about genomic profiling?

Dr. Tomlins: Genomic profiling is testing the patient's tumor to determine what DNA changes are present in the tumor that differ from the patient's DNA in all of the other cells. These are called somatic genomic alterations, somatic meaning they are coming from the body. These are changes that are occurring in the tumor; therefore, they can't be passed on. They're not heritable, so they don't have the same implications as genetic changes. Instead of talking about how should we counsel the patient and their family, somatic alterations are relevant for the treatment of the tumor. You're looking for changes that are present in the tumor only because those often make effective therapeutic targets. The therapy is going to have fewer side effects if it just impacts changes in the tumor and not in the rest of the cells in either the prostate or the rest of the cells in the man's body.

DNA repair genes are also the most relevant class of genomic alterations in prostate cancer, including both the 1) HRD genes: BRCA1, BRCA2, and ATM; 2) and the mismatch repair genes: MSH2, MSH6, MLH1, and PMS-2.

Importantly, the HRD and MMR genes can be impacted by both genetic and genomic changes. So these can be altered by genetic changes the patient inherits and has in every cell in their body, or they can happen only in the tumor. Detection by a genetic test has implications for siblings and children, and also has therapeutic importance. Detection by a genomic test has implications for therapy; however, many genomic tests do not distinguish between genomic and genetic events, and it's important that men with prostate cancer have both genetic and genomic testing. No matter how a man has a defect in these DNA repair genes, genetic or genomic, the therapies directed against HRD or MMR appear to be equally effective.

Therapies called PARP inhibitors specifically target the HRD pathways. Genetic or genomic changes in BRCA1 or BRCA2 (there's about 10 other genes, including ATM, that, depending on the PARP inhibitor therapy, may also be indicated) may lead to a recommendation of therapy with PARP inhibitors. Olaparib and rucaparib are FDA approved for men with metastatic prostate cancer who have already received anti-androgen therapy. Rucaparib is approved in men who have also had second-generation anti-androgens as well as chemotherapy, while olaparib is also approved prior to chemotherapy.

Those are the therapeutic implications of a BRCA1 or BRCA2 mutation. Whether they're picked up by genetic or genomic testing, they lead to the same treatment recommendations, and thus testing for these biomarkers for men with metastatic prostate cancer are recommended by the NCCN.

Therapies called checkpoint inhibitors, which unleash the immune system to fight cancer, specifically target the MMR pathway. Such immuno-oncology therapies, which have revolutionized the care of many cancers, appear to work in a very small subset of men with prostate cancer, specifically those with dMMR. But importantly, about 2% to 5% of men with metastatic prostate cancer have dMMR. In prostate cancer, dMMR is much more commonly somatic, meaning it's only occurring in the tumor, than a genetic change. Hence, genomic testing, whether by immunohistochemistry for evaluating the MMR genes, next-generation sequencing including MMR genes and the phenotype of dMMR, or specific dMMR testing (usually called MSI testing), is indicated for all men with metastatic prostate cancer. Like HRD, dMMR, regardless of whether it's detected by germline or genomic testing, will likely lead to the same therapy (the checkpoint inhibitor pembrolizumab). If dMMR is detected by a genetic test, that will lead to both genetic counseling and the family implications, but therapy-wise, they're the same.

Unfortunately, this is not a simple thing where you can do one test and know exactly what you should do. A genetic test can tell you about the inherited risk and it can inform on therapy, but it will not identify all men that may be eligible for therapy. Likewise, if a genomic test only tests the tumor and detects HRD or dMMR, it doesn't usually determine whether the change is actually genetic or genomic, and follow-up genetic testing should be performed. That's why the recommendation is to do both genetic testing and genomic testing for men with metastatic cancer.

Where does Strata's testing fit into the paradigm?

Dr. Tomlins: Strata does genomic testing of the tumor tissue, and we started with the belief that all patients with cancer deserve to know the genomic profile of their tissue. There are a variety of different ways to do genomic testing for men with prostate cancer. You can test the prostate cancer tissue itself or you could do testing from cancer DNA that is shed into the blood (a "liquid biopsy"). Such genomic testing can be complemented with genetic testing on normal tissue, which is usually from the blood or from the cheek.

Our experience is nearly all men in the United States are going to have a tissue-based diagnosis of prostate cancer, largely for diagnostic and insurance reasons. Even men that have very, very, very elevated PSA, even if they are presumed to have metastatic disease, usually still undergo a tissue biopsy to confirm that diagnosis because some other things can masquerade as prostate cancer. So we focus our efforts on doing genomic testing on the tissue. We test for the HRD alterations, as well as dMMR through multiple approaches, and we also test for other genomic alterations that may confer eligibility for clinical trials. Some specific HRD alterations (such as complete loss of the BRCA2 gene), can more often be assessed in tissue than in cancer DNA in the blood, so that's why we've focused on tissue testing.

Importantly, even though genomic testing is just testing the tumor, we are able to detect both genetic and genomic changes. We can't tell whether these changes are genetic or genomic, but if you have a change, no matter whether it's genetic or genomic, that's going to lead to the same therapeutic recommendations. Although we don't do genetic testing at Strata, we believe every man with metastatic prostate cancer should get genetic testing, just as we believe that they should get genomic testing. We've found that there are many barriers to adoption of genomic testing in prostate cancer, including the difficulty regarding genomic versus genetic changes, so we've worked very hard with healthcare systems to address these types of barriers so they can implement genomic testing for all patients with metastatic cancer.

Is it only done on tissue obtained from the biopsy? Do you sometimes test tissue post-radical prostatectomy?

Dr. Tomlins: We test the full spectrum of prostate cancer tissue. So that could be diagnostic biopsy or it could be radical prostatectomy. It could be a liver or lung biopsy to confirm metastatic disease. Prostate cancer frequently metastasizes to the bones, so you have to be able to test these biopsy samples as well, but they require a special processing. Any man who is undergoing a bone biopsy for prostate cancer should make sure their oncologist notes when they order the test that it's for genomic evaluation, so when the the biopsy is performed (usually by interventional radiology), they will know to treat the tissue for genomic analysis.

Some men with later-stage metastatic disease may undergo biopsy to determine if their prostate cancer has changed to the type of prostate cancer that is no longer dependent on the androgen receptor. That may change the therapy recommended. The tissue obtained during that procedure can also be used for genomic testing. We've worked really hard to optimize our testing to work on the full range of tissue samples.

An important thing is the more recent that tissue, regardless of the type of genomic test being done, the better the test will do. If a man is diagnosed with metastatic disease, their current tissue at the time of diagnosis is highly amendable to testing by Strata or other types of testing. If a man with a diagnosis of lower-grade disease had a radical prostatectomy and 15 years later is having a PSA recurrence and is deemed to have metastatic disease by either that PSA recurrence or by imaging, it's often much more challenging to profile that original 15-year-old tissue sample.

In those cases where the tissue may be more than five or 10 years old, strong consideration should be given to getting a new biopsy for genomic analysis at the time where that may influence the therapy. They may also consider other testing modalities such a liquid biopsy; however, that testing often works best when men have a large metastatic burden because that means that there's more likely to be enough cancer DNA in the blood for testing.

This can be a very challenging scenario regarding the best type of testing to do when there isn't recent tissue available.

Could you envision a time when we do genomic profiling tests on every man who has a biopsy that tests positive for prostate cancer?

Dr. Tomlins: Certainly with metastatic cancer. The guideline

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recommendations right now say, "Any man who has metastatic disease." Not everyone has that at the time of diagnosis, but certainly, anybody diagnosed with what we call de novo metastatic disease, where they present with metastatic disease, should be tested.

Genomic testing is covered by Medicare in that scenario for all patients with advanced cancer regardless of whether it's prostate cancer or another tumor type. Specifically in prostate cancer, I strongly recommend genomic testing because identification of HRD or MMR defects will change the course of a man's care at some point in their treatment journey. It may not change their first-line therapy, but it will almost certainly change recommendations for later lines of therapy. It will also make them eligible for new clinical trials testing agents targeting HRD and dMMR earlier.

I feel it's better to do genomic testing on the tissue sample at the time that it's taken because that will give you the highest quality profiling. For example, a man with newly diagnosed metastatic disease may receive standard androgen deprivation therapy, have a very strong response to it, and not need additional therapy for two or three years or even longer. But there's a risk that if the tissue is not tested until three to five years later, it may give us a suboptimal profile. There may be clinical trials with strong, compelling rationales that if the man knew he had one of those defects, he may choose a different either investigational or standard of care therapy course.

Coverage decisions and recommendations for genetic testing in prostate cancer vary, from those that only cover or recommended genetic testing at the time of metastatic disease to those that base this on the family history or the presence of aggressive localized disease (for example men with Gleason score >=8 or Grade Group >=4).

I personally think men with aggressive localized prostate cancer and metastatic cancer should get genetic and genomic testing. Genetic testing because of the implications for relatives and screening for other cancers. Genomic testing because you could find they had one of these alterations that may change either how you choose to follow that man or may confer eligibillty for earlier stage clinical trials. If you find HRD or dMMR before radical prostatectomy in men with aggressive disease on biopsy, that may impact neoadjuvant or adjunct therapy consideration, particularly with clinical trials. At present, standard of care treatment wouldn't change if a man with aggressive localized prostate cancer had a HRD or dMMR alteration, which is the argument for not doing the genomic testing upfront, but I think over the next few years that may change as some of these therapies move forward toward the adjuvant or neoadjuvant setting.

How long does it take to get results? How much does it cost if a man has to pay out of pocket?

Dr. Tomlins: Typically, the patient's physician orders the test from Strata. After receiving the tissue from the pathology lab, it's about eight business days before they will get the results back.

For men with metastatic prostate cancer, Medicare will cover tissue-based genomic testing, with both Strata tests or other tests that have been technically evaluated by Medicare. For patients who don't have Medicare, Strata and other testing providers have a range of contracts with different private payers that may or may not cover this kind of testing. Again, there are NCCN guidelines recommending this specifically in prostate cancer, so I think there's clear evidence to support that.

We started Strata with the belief that everybody deserves genomic testing, so cost should not be a barrier to anybody with metastatic prostate cancer getting Strata testing. We have financial assistance programs, and the vast majority of patients will qualify for financial assistance. The majority of those patients would not pay more than $200 or $300 out of pocket.

What about men outside the United States?

Dr. Tomlins: It depends on the country the man is in. Some countries have laws preventing sending tissue outside of the country, so you would need to use an in-country provider. At Strata, we only offer testing in the United States.

For men outside of the United States, it's the same sort of process to order the tissue. Things are a little bit different in terms of what their country may cover. Nationalized insurance may cover testing, but it may not. We at Strata deal with those on a case-by-case basis.

Any other thoughts for men who may be reading this?

Dr. Tomlins: There are different kinds of genomic tests that can be used in different tumor types. In some tumor types, we can look for a single variant. We know exactly what we're looking for. Those types of tests are usually a little bit easier to do. The type of testing needed in prostate cancer to detect HRD and MMR gene alterations are a bit more technically challenging. It's important if you're considering getting genomic testing to make sure you understand the content of that test, and that those types of alterations can be tested for.

Those types of tests, including the type we do at Strata, can also identify additional alterations that are not associated with approved therapies but may be associated with therapies that are in development, investigational therapies. There are also some very rare alterations that have associated therapies regardless of cancer type. Those are exceptionally rare and are rarely found in prostate cancer. I always say that is the reason to get tested because, although they're very rare, if you have one of those, that will dramatically change your treatment course. I think strongly that every patient deserves to know if they have one of those. With therapies being linked to genetic or genomic changes, the push for testing has become much bigger in the past five years. Many clinicians, ranging from urologists to medical oncologists, aren't that familiar with some of these therapies.

Also, the difference between genetic and genomic changes can be confusing. I think there's been underutilization of these tests for those reasons. That's why I think it's important for men to advocate to get both kinds of testing. A variety of groups such as the NCCN, National Alliance of State Prostate Cancer Coalitions, and the International Society of Urological Pathology have information saying, "These are the types of testing that should be performed, particularly in men with metastatic cancer." I think it's important for men to advocate for that. If they asked their doctors, "Hey, if you had this, would you want to know if you had one of these alterations?" They should say, "Yes." If they don't, they aren't aware of the latest recommendations and approved therapies. But there shouldn't be logistical or provider interpretation barriers for getting that kind of testing done.

A man should know that just because he hasn't been offered the testing that doesn't mean it's not appropriate for his case?

Dr. Tomlins: Correct. The first thing they would do is just ask their clinician. I think having that kind of information and asking them, "Is this type of testing relevant for me?" Anybody with metastatic disease should get both genomic and genetic testing. The guidelines are fairly clear about that, so I would expect most clinicians should be aware of that. If they're not, I think most of them would be willing to perform the testing, understanding that some of them may not be the best at interpreting these tests. That's something you can always ask the testing provider. So if a man is confused about whether genetic or genomic testing is indicated, the first step is to ask the physician. The next step would be contacting one of the testing companies directly and asking. We know the criteria for to ask about, "Do you have metastatic cancer?," et cetera.

Some physicians may push back at testing early in metastatic cancer by saying, "We've started you on the standard of care therapy. There's nothing we would do differently if we knew this information at this point in time." I think that's fair, but I'd want to see a clinician who followed that with, "But let's definitely consider that if the aggressiveness of the cancer changes or if the first therapy stops working." That's the time to advocate, any time a change in consideration is being made in terms of therapy: "Is this the right time to do genomic testing?" My bias is to do that as early as possible, so you have that information.

I suppose the earlier you ask the question, the earlier a provider knows that you're open and interested in that kind of testing. Who knows, maybe there's a clinical trial.

Dr. Tomlins: Exactly. Both PARP inhibitors and checkpoint inhibitors were found to work in men that got genomic testing and participated in a clinical trial. Genomic testing is the only way to find several of these alterations, and it was only by men participating in these clinical trials that we know the drugs work and they were approved. Knowing that full genomic profile as early as possible allows for consideration of both the standard of care path, as well as compelling clinical trials. That is what I would want for myself or a family member. Likewise, knowing the genetic profile is important both from the therapy perspective as well as thinking about the implications for relatives.

Pp[1]

Robert Reiter, MD
Testing for Prostate Cancer

Dr. Reiter is the Bing Professor of Urologic Oncology and Director of UCLA's prostate cancer program.

His clinical and research interests include improving management of prostate cancer using functional MRI and molecular imaging of the disease, robotic prostatectomy, molecular biology of prostate cancer progression, and precision medicine and clinical trials for management of high-risk and metastatic prostate cancer. Dr. Reiter is involved in all aspects of urologic oncology, with an emphasis on prostate cancer, and brings extensive experience in robotic surgery and the applications of translational research and the latest in MRI and molecular imaging to the management of men with this disease.

He is Principal Investigator on UCLA's Prostate Cancer SPORE, a $12 million federal grant that is focused on translational research in prostate cancer.

Prostatepedia spoke with him about testing for prostate cancer across the disease spectrum.

Which tests is a man likely to encounter for prostate cancer?

Dr. Reiter: It's an increasingly complex field because there are many new tests being introduced that are purported to be superior to PSA. They are competing in a landscape with better imaging using MRI, which has been shown by us and others to have excellent characteristics for identifying and diagnosing prostate cancer. But no single test is perfect. The question is really, how do you integrate these? Do you need to integrate these? Which is the best? Which is the best pathway? And it's interesting because there's a trial that we're just writing and putting together and trying to get funding for to address how to optimally test for prostate cancer. But let's start with PSA.

PSA screenings have been around now for a long, long time. It's still very good, but the scuttlebutt on PSA has always been that it's positive in a large percentage of men who don't have cancer. Also, many men who have an elevated PSA and have a biopsy end up having low-grade cancer and consequently are at risk of getting overtreated.

As you probably know, the US Preventive Services Task Force several years ago gave PSA a grade of D, which basically meant they did not recommend it. However, the consequences of this have been reduced PSA testing and reports of increasing incidence of locally advanced and metastatic disease at presentation. While it is difficult to ascribe cause and effect to the reduction in testing and the diagnosis of more advanced disease, it is a concern.

In my own experience, I am seeing far more men with high grade, locally advanced and metastatic disease than I saw 10-15 years ago. I almost never saw somebody who presented with advanced disease. Now I see that virtually every week. And it's borne out to some degree by a number of publications that have come out that have shown that the stage migration that happened from high to low risk in the '80s and '90s because of PSA, shifted back now to almost a pre-PSA era.

It gets to the basic premise: Is there a value in PSA screening? And I think the Task Force basically said, no, it's not valuable because you overdiagnose so many. You treat so many to help a small percentage that you can do more harm than good. Because of this, the field has focused for the last 10 or 15 years on what we would term "smart screening." Number one is determining who should be screened, who should be tested, at what age they should be tested, and what the thresholds are for doing additional diagnostics, such as MRI and biopsy, with the hope of essentially weeding out those who may have low-risk disease to find people with more significant cancer.

I think that there are many ways to do that. There are numerous risk calculators you can use that essentially integrate PSA, age, family history, things like that. That's one form of early screening you can use.

There's a ton of literature about PSA at age 40 — a single PSA at age 40 being a very strong predictor of subsequent prostate cancer. I think the cutoffs are somewhat variable, but men who have a PSA less than one at age 40 have a very — not zero — but a very low risk of developing prostate cancer over the next 20 to 30 years. Whereas, a person who has a PSA greater than one has a significant chance. And that can inform how often you should get tested with PSA.

We still use things like PSA velocity, which is the change in PSA over time. All of those things help to use PSA in a better way. Of all of them, I would say the best way to use PSA in this day and age is something that was first described about 25 years ago, which is called PSA density. PSA density is the PSA divided by the size of the prostate. And it's a very strong predictor of, not just prostate cancer, but "significant" prostate cancer. There are numerous tools, without even using any modern technologies, to help screen smarter, because that's the motto: screen smarter.

On top of all of those things, there has been the development of both biomarkers, and, of course, imaging. I've been mostly focused on imaging during my career, but also very interested in biomarkers.

"Are we changing the game in the right direction?"

The biomarkers that are in use now are numerous. There are two types.

One is on the horizon, but not used so much right now, called polygenic risk scores. We know that prostate cancer in a significant percentage of men is inherited, but it's a very complex inheritance pattern. You can ask a man if they have a brother or father with prostate cancer, which certainly says you have an increased risk of prostate cancer. But now we know much more about the genetics. There are several different companies that have developed and are developing so-called polygenic risk scores that survey a comprehensive panel of what are termed SNPs (single nucleotide polymorphisms), which are basically variants of segments of the genome that have been associated with specific diseases such as prostate cancer. It's another way to say which person should be followed intensively, should be screened with PSA and other tests intensively, and which patients you can possibly screen less often because they have lower risk.

So those are very much in development and on the horizon. And I think they show great promise.

On the other hand, we have serum and urine biomarkers, such as ExoDx, SelectMDx, 4kscore, and a few others. 4k is a blood test that measures PSA and a number of other kallikrein-related proteins. All these different PSA isoforms that exist within the blood and are associated more with cancer than normal tissue.

4k is an example of a test that can be used in conjunction with PSA testing. A common example I see every day is a guy who has, let's say, a PSA of 6, and maybe I'm not so suspicious that I'm going to recommend a biopsy immediately. I might get a 4kscore first. And the 4k will give me the likelihood that this person has prostate cancer and the probability of having significant prostate cancer, which is defined as Gleason 7 or Grade 2 or higher.

There's a threshold that the test uses, which is, I think, about 7.5%. If it's above 7.5% likelihood that you could have significant cancer, the physician could say, "I'm going to do more workup, maybe a biopsy, or MRI and a biopsy." Whereas if it's less than that, you could just monitor the PSA or monitor a 4k over time.

Same thing with SelectMDx. It gives you a likelihood of having significant prostate cancer. It also uses the threshold value to say likely or unlikely. Both of them are promising because they both have pretty high areas under the curve. That means that the tradeoff between over and underdiagnosis is just about right, versus PSA, which has a very low area under the curve. It's just statistics.

I think an easier way to look at both of those tasks is you're trying to say,

"Among this population of men who have an elevated PSA, can I weed out those who are incredibly unlikely to have cancer?" That's the negative predictive value. If you have a very high negative predictive value, that means that your probability of having cancer is very low. Both of these are reported to have negative predictive values between 80 and 90%, even as high as 95%. So, if you see a man with an elevated PSA, and they've got a normal or low SelectMDx or an ExoDx, which are urine tests, or a 4k, which is a blood test, then you could probably just monitor that person and not interrogate them further.

There are a number of biomarkers. They've never been compared head-to-head. They've never been used together in conjunction to see whether they perform better than a single one alone. But I think they're very useful. That's on the biomarker side.

MRI is another biomarker. It is a very sensitive test for detection of significant prostate cancer. There's debate about how sensitive it is or how accurate it is. I'd say 80% and even as high as 90% of men who have a significant prostate cancer will have some abnormality on an MRI. You can imagine if somebody comes in with an elevated PSA, particularly if you're suspicious they have cancer, just going right to an MRI is a good way to go. We've published extensively on using MRI as the first test after PSA.

A man comes in with an elevated PSA? Get an MRI. If the MRI shows a lesion, you biopsy that lesion. If an MRI does not show a lesion, you could either just observe, or you could do one of the biomarkers we just talked about to be sure that you didn't miss something in those 10 or 20%. Or you could just do PSA density. There are many papers out there that say that if you have a negative MRI and you also have a low PSA density—which can be easily measured because the MRI provides you with the exact size of the prostate—the likelihood of having significant cancer is less than 7 or 8%. Really, really low.

But if it's higher than a threshold of 0.15, then you should probably still be biopsied even if the MRI was negative. So now we've got a plethora of good ways to improve PSA and reduce the number of unnecessary biopsies. If you use a biomarker and it's negative, you're reducing the number of unnecessary biopsies by anywhere from 30 to 50%. With MRI, you're also reducing significantly the number of unnecessary biopsies.

A big question has been whether MRI is needed prior to biopsy in men with an elevated PSA. There was a large international study called Precision that tested the comparison of MRI followed by targeted biopsy versus just standard biopsy, showing that MRI-targeted biopsies increased the diagnosis of significant cancer, while reducing the number of biopsies needed. I think it was 20 or 30% and it increased the likelihood of just finding significant cancer and reduced the likelihood of finding low-grade cancer.

In Europe, an MRI-first strategy prior to biopsy was accepted as standard of care a few years ago. The American Urological Association now says more or less the same thing. It's been our practice at UCLA here for about 13 years. I think most people would agree that one should not have a biopsy without an MRI first. There's still some debate in this country, and it's not written in stone.

What's the nature of the debate? Is it a cost-effectiveness or access issue?

Dr. Reiter: There's probably a cost issue. There's probably some access issue, too. Some insurance companies still will not cover an MRI first, but that's not something that's rejected too often anymore. I think some people aren't believers; there's still plenty of naysayers out there. There's definitely what we call interobserver difference regarding MRI. Put three radiologists together in a room and they may not agree. But I would say that as time has gone on, the quality and the performance have gotten better and better as radiologists and urologists have been trained. I think that's less of a problem now.

Then, the question is: What's the best approach? I've got good old-fashioned risk markers based on family history, PSA, PSA density, which is such a good test. Those are simple, cheap, and pretty effective. I've got biomarkers, which are not cheap but are probably cheaper than an MRI. And then I've got MRI. What's the right way to integrate them? There was one study published, I think from UCSF, that suggested using a biomarker first might reduce the number of biopsies even more than doing an MRI first. It's a retrospective study, but it's intriguing. The best sequence of tests to diagnose significant prostate cancer and reduce the number of biopsies required is still not known.

Wouldn't biomarker first be more cost-effective?

Dr. Reiter: Probably, but it would depend on the health system. In the UK, an MRI is around $250 or less, whereas here it can be $1,000 to $2,000. These biomarkers can cost $500 or more, so the economics may be different in different places.

In the future, people are going to get a PSA at a young age. They're going to get a polygenic risk score, and that's going to determine how often they get PSAs checked subsequently. Then if they have an elevated PSA at a later age, or if there was a change in PSA, people will either go to one or more biomarkers first or they'll just go straight to MRI and use them interchangeably or in an integrated fashion in some manner. I think we will continue to optimize the diagnosis so that we're capturing those who need treatment and not overdiagnosing those who do not.

Do you have any interesting anecdotes about testing you can share?

Dr. Reiter: The way that I do it generally is that if I have a low suspicion that a patient has cancer, I don't put him through an MRI. I would obtain one of these biomarkers or look at their PSA density. If they are negative, I simply monitor them yearly. If I am pretty suspicious based on family history, PSA velocity or density, then I go right to the MRI, and it seems to work pretty well. But I want to see which of these is the right strategy because you can't do everything on everybody. It's cost-prohibitive.

Right.

Dr. Reiter: We just got PSMA PET approved and have been doing it for four years. I personally use that mostly in men who have higher risk cancers to determine whether they've got metastatic disease or localized disease.

We just submitted a paper comparing PSMA and MRI for staging. It showed they are somewhat complementary. PSMA may do a little bit better job of delineating the extent of the cancer—is it unilateral or bilateral, versus MRI, which underestimates how big a tumor is. And that's important if you're thinking about doing some of the newer kinds of focal types of treatments versus radiation or surgery. I think PSMA is going to be used more in staging of early-stage cancers in the future. PET/MRI machines are coming out, but they're cost-prohibitive right now. PSMA is still only approved in two places in this country. But it will be approved, I'm sure, within the next six months around the country because there is a company behind one, and then there are additional companies developing other PSMA tracers.

And that will be a game-changer.

Dr. Reiter: We're going to see a lot more. I think it's going to be a mixed blessing. I've spent the last few years talking about PSMA and what I've learned over the last five years of doing this is, in a way, it's the game-changer we've always been looking for, but it is now raising more questions than we can answer.

What do you mean by that?

Dr. Reiter: Let's say you see a person with a high-risk cancer and he's got a PSMA-positive lymph node. Historically, you would've assumed that person did not have metastatic disease and you would treat with hormones and radiation or you would treat with surgery. There's debate about which of those is the best approach, obviously.

The alternative would be if they have a PSMA-positive scan and you say, "Uh-oh! They've got a lymph node. That's positive. Should that change my management? Should I forget about surgery now and say that it has no role to play. Should I boost radiation just to that lymph node that I see or give it more broadly? Should I use hormones alone?" And we don't know the answer, because what's happening is that patients we used to consider nonmetastatic, we now call metastatic. The high-risk patients who we didn't know if they were metastatic or not, all of our trials are based on all that old data. It's stirring the pot because we're now talking about apples and oranges.

The other thing that's happening a lot is when you have a hammer, the whole world looks like a nail. When patients have these scans and it turns out, let's say, they've got three spots in lymph nodes, historically, you probably would have just treated with systemic treatment. Hormones or whichever. But now, physicians are tending to go after each one of those with radiation in a kind of whack-a-mole fashion. There is some data that this is a valid approach, delaying time to disease progression. But the jury is still out. So basically, while we are staging cancers more accurately, how and whether that should impact treatment decisions remains unknown.

While it's a game-changer, the question is: Are we changing the game in the right direction? Pp1

Ashley Ross, MD
Genomic Testing After Radical Prostatectomy

Dr. Ashley Ross, Associate Professor of Urology at Northwestern University, is a surgeon scientist who specializes in urology and urologic oncology and is a nationally recognized expert in prostate cancer. His research efforts focus on the development, testing, and implementation of novel diagnostics and therapeutics with a goal of reducing the suffering from prostate cancer.

He spoke with *Prostatepedia* about genomic testing for prostate cancer and Decipher after prostate cancer surgery.

Which genomic tests are available to men with prostate cancer?

Dr. Ashley Ross: Genomic tests are mostly used and available for localized prostate cancer and for prostate cancer patients who have undergone a surgical resection or prostatectomy. Genomics is the study of genes. "Genomic tests" is often used as a catchall term to refer to multigene RNA-based signature tests.

There are three commercial tests that look at multigene signatures at the RNA level that are all prognostic of prostate cancer risk. Those three tests are Myriad's Prolaris test, which gives you a cell-cycle progression score, the Oncotype DX prostate score, which gives you a genomic prostate score, and the Decipher test, which gives you multiple signatures, but a genomic classifier, in particular.

"Genomic tests are mostly used and available for localized prostate cancer and for prostate cancer patients who have undergone a surgical resection or prostatectomy."

If we look across the disease space, these tests are primarily used in localized prostate cancer. For low-risk or favorable intermediate clinically localized disease, these tests can help men decide whether or not to pursue active treatment or conservative management strategies, such as active surveillance or, in some cases, watchful waiting. All three tests have been used fairly extensively in that situation. They provide information that's both independent from clinical pathological features and can help inform you of the risk that the man may progress, if they're put on surveillance, or may harbor what's called "adverse pathological features," like having a higher Gleason score or having disease that is microscopically outside of the prostate.

The tests aren't fully interchangeable, but there was a nice study done a few years back that showed that most of the different signatures of disease risk, when considering low-risk or favorable intermediate-risk patients, seem to track together, and that patients that have very high scores are going to have worse outcomes and maybe are not appropriate for surveillance. When you go then to intermediate-risk prostate cancer or disease after treatment, the test that, in my opinion, has the most directed evidence is perhaps the Decipher genomic classifier test.

The question gentlemen with intermediate-risk prostate cancer usually have is if they treat with radiation, should they intensify by adding androgen deprivation therapy or not? One retrospective series of intermediate-risk patients showed that if they got radiation alone and had a low Decipher genomic classifier score, the eight-year metastasis-free survival rate was 100%. So the patients did very well. But, if they had higher or average genomic classifier scores, then they would have some metastatic events.

Furthermore, some of the high-risk patients, even if you give them full therapy with androgen deprivation and radiation, will have some recurrences, so maybe they need more intensification.

For intermediate-risk prostate cancer patients, the idea is that you could use these genomic tests, particularly Decipher genomic classifier, to decide whether or not you need a hormonal therapy with your radiation if you're going to take that treatment route. That still has to be prospectively validated. There's an ongoing NRG Oncology trial called Guidance, which is going to study that in a prospective fashion.

Are they still taking patients for the trial?

Dr. Ross: Yes. They are.

The next question is, how about for high-risk prostate cancer? I don't use this test as much in that space, but there are clinical trials looking at intensification of hormonal therapy for high-risk and very-high-risk disease. That trial is also using the Decipher genomic classifier to identify men who would be at highest risk and may benefit from more intensification of their radiation therapy with elements like Xtandi (enzalutamide), for example. That trial is also, I think, open and accruing.

After prostatectomy, again, it's a Decipher genomic classifier that has the most evidence. There's a nice meta-analysis and data review published by Dr. Dan Spratt and his colleagues that goes over the evidence. There are over 12,000 patients with long-term outcome data available that show the predictive power of the Decipher human classifier in that setting.

It is important in decision-making about salvage radiation versus adjuvant, or we could say very early salvage, and also about use of hormonal therapy.

"It's a Decipher genomic classifier that has the most evidence."

Earlier this year, National Radiology Group published a paper showing that if you're getting salvage radiation and you have a lower PSA, the Decipher genomic classifier can be an important tool to determine whether you should get androgen deprivation or not. Patients in the randomized trial who got radiation therapy with hormonal therapy and had low PSA, below 0.7, were actually harmed if their Decipher score was low. They were being overtreated and overall survival was less. Whereas if the Decipher score was high, they benefited in overall survival and in cancer-specific survival. That study has made the Decipher test, I think, a must-have in the post-prostatectomy setting when you are considering salvage radiation. That's pretty much how we use genomics across disease space.

Interesting. You mentioned that in low-risk patients, the Prolaris and Decipher tests help determine whether to take the path of either active surveillance or a more aggressive treatment. Is it also used as a monitoring tool for when to take men off active surveillance?

Dr. Ross: I would say it depends. For example, if you're on surveillance for low-grade cancer and I biopsy you the next year and you have more low-grade cancer, could I then run the genomic test to determine that if, though the pathological grade has remained the same, your cancer has a higher genomic classifier score, that you should come off surveillance? It can be used in that way, for sure. In reality however, if the cancer stays at the same risk level and there are similar amounts of the same grade cancer, I usually do not obtain serial genomic testing. In an ideal world, we could do that, but to date, most of the insurance companies will not allow serial, meaning routine, frequent testing of the same individual when their cancer disease risk hasn't changed.

I think if you are an individual who's currently on surveillance, particularly if you're borderline for surveillance and you've never had such a test ordered, you should have that test ordered and it may influence the decision to take that man off surveillance. In my practice, what I usually do is send the genomic testing upfront at initial diagnosis to determine if surveillance is appropriate for you. That testing helps determine if surveillance is an option that will be sustainable, not just for one year, but likely for three to five years.

Do you suggest that men ask their doctors about getting the Decipher test

post-prostatectomy if it's not already offered as routine?

Dr. Ross: After prostatectomy, if your PSA has become elevated —0.2 or greater—the data is suggesting we should get a Decipher genomic classifier test so we know how to give salvage radiation therapy. This is based on the recently published findings from a genomic analysis of NRG Oncology's RTOG 9601 trial. RTOG 9601 was a randomized Phase III trial that provided level one evidence about hormones with salvage radiation. They've now done a subset analysis of a mix of over half those patients that showed the benefit of using Decipher in decision-making, meaning that it's a crucial factor to determine, are you going to harm or help the person by adding hormonal therapy.

For patients after prostatectomy that do not have an elevated PSA, the PSA is below 0.2 or below 0.1, there's less evidence about the absolute need for testing like Decipher. I think there's some good evidence from lots of retrospective evaluations, but there's not this level one tied-in evidence that makes it a must-have. I think it certainly adds value. I do it routinely in my practice for patients with PSAs between 0.03 and 0.1 to help me with decision-making. There are good arguments to do genomic testing upfront if your patient has adverse pathologic features of prostatectomy, whether those be extraprostatic extension, lymph node involvement, or positive margins. But in terms of me saying, "Where would I give an absolute recommendation?" I think now with the publication of the 9601 trial, the must-have place for Decipher genomic classifier testing is in men with PSAs that are detectable after prostatectomy who are considering salvage radiation. The reason it's a must-have is to help you with a decision about using androgen deprivation therapy as an adjunct to that or not.

Any last comments for men reading this?

Dr. Ross: We're now kind of taking a large step into the era of molecular medicine, not just in prostate cancer, but in most aspects of medicine. In prostate cancer, in particular, there are these clinical-grade genomic tests that have high utility in localized prostate cancer and in treatment decision-making for men with prostate cancer after they've had a prostatectomy. We also have multiple genetic tests available and those genetic tests all have a high utility in men with metastatic, particularly castrate-resistant prostate cancer, where it's paired to precision medicine as well.

Most physicians will be aware of these things, but make sure you ask about molecular testing. For localized disease, talk to them about what can we learn from these genomic tests. For metastatic disease, talk to them about what can we learn from genetics. Ask them why you got your prostate cancer. Was there a genetic risk present there? And realize that the tumors are not just their Gleason scores, their histopathologic diagnosis. We are really in the era of molecular medicine, and that allows us to be more precise and make the best treatment choices for you, the patient. Pp

Sam Salman
Urine-based Liquid Biopsy Testing

Sam Salman is the CEO and co-founder of miR Scientific, a company that developed an FDA-designated breakthrough, urine-based, liquid biopsy test for the detection and risk classification of prostate cancer.

Prostatepedia spoke with Mr. Salman about miR's testing platform and how the tests fit into the greater paradigm of detection methods for prostate cancer.

How does the liquid biopsy urine-based test you have developed work? What is its mechanism of action and methodology?

Mr. Sam Salman: We have developed a true liquid biopsy platform. The purpose of the platform is to handle a disease that affects virtually every man over 45, prostate cancer. Our platform integrates several elements of the current standards of care into one event, noninvasive urine collection. We're meeting a need of being able to identify patients who have disease and then identifying the type of disease to allow treatment to start right away, which can influence positive outcomes.

A patient provides a urine specimen, which is then sent to our lab. We interrogate certain elements of information excreted from cells throughout the entire prostate. A biopsy samples a section of the patient's prostate. The needle may happen to intersect a tumor core and the information that's derived in that biopsy is from the sum of those tumor cores, right? The needles provide a view of parts of the prostate effectively, not the entire prostate.

"We have developed a true liquid biopsy platform."

Our liquid biopsy is truly a liquid biopsy in that we're identifying small noncoding RNAs (sncRNA) that are excreted from cells throughout the prostate using a highly conserved mechanism called the endosome/exosome pathway. In essence, cells excrete materials. One of the materials they excrete is this class of sncRNAs, and they come from different parts of cells and all cells in the prostate produce them. They're encapsulated in exosomes, which are effectively fragments of cellular materials and they're very stable. The RNA that we're capturing is micro. The smallness of them gives them an inherent stability.

When these sncRNAs get excreted, they primarily end up in the bladder; they do not end up in the bloodstream at this point. It's passed through urine, so this is a fully noninvasive approach—urine. We're interrogating materials that come from throughout the prostate, throughout virtually all cells, healthy and unhealthy. We're then capturing those from the specimen that the patient provides. We then go through a very sophisticated process to interrogate the materials that we believe are highly informative, not only to say whether there's cancer or not, but whether the cancer is low, intermediate, or high risk.

These risk classifications are the same type of risk assessments that are derived from pathology and clinical risk scoring and even anatomical analysis. They provide information about what a patient needs to do next. If the patient is assessed through our platform as having either low- or intermediate-risk disease, this is only from urine. All that has happened is a patient has provided a urine sample. The patient and their care provider at that point can determine if they only need to be monitored for biochemical progression. This monitoring is referred to as active surveillance and represents the ability of the patient to avoid interventions such as core biopsies or even therapeutic interventions such as prostatectomy or radiation while the patient is monitored on an ongoing basis as follows.

Monitoring is done from another urine specimen, which can be collected three to six months in the future, depending on the discretion of the provider. If there is a change in their miR Sentinel signature (the profile of the expression levels of these sncRNAs), for example, if their risk group changes from low-risk to intermediate-risk, then the patient should go and do what they would need to do next—intervention-based assessments, biopsy, MRI, etc. If the first urine specimen determines the patient has high-risk disease, which we can classify from only the urine, then obviously that patient needs to be prioritized for biopsy and likely would receive definitive treatment.

Our test effectively eliminates several friction points for the patient to understand what they have and what they should do next. We call this a disease management platform, which is a different approach than what's available right now for managing a patient from the very beginning to the point in which they can take definitive action to create the best possible outcome for themselves.

We have two parts of our platform. We have our discovery platform that determines which RNA entities of the many thousands available to be analyzed are actually relevant to figuring out which is cancer versus no cancer, but then is it low-risk, intermediate-risk, or high-risk? Once we determine which and how many of those different types of sncRNAs there are, we then put them on a high-throughput platform to enable us to more rapidly respond to a patient's urine coming in. The high-throughput platform involves only the interrogation of the informative RNAs through what's called real-time PCR technology.

The PCR technology interrogates the separated RNA. We analyze that data and the result comes back as only one of four responses: no molecular evidence of prostate cancer, low, intermediate, or high-risk molecular evidence of prostate cancer. The word "molecular" here is used to differentiate from pathology in the sense that we're looking at the molecular profile of each cell that excretes materials to either say they're healthy or showing some measure of malignancy.

We're effectively providing a molecular measure of malignancy. To put this into context, we published data in the *Journal of Urology* in September of last year. We broke down the different attributes of our test, including our discernment of no cancer versus cancer, as well as our discernment of the type of cancer by risk: low, intermediate, or high. We analyzed a cohort of around 1,436 patients. When we combined the specificity and sensitivity, which are the measures of how effectively true cancer is identified, and a true non-cancer is also identified, so eliminating false positives and false negatives. We're in the 90s.

We have what we and many national experts consider to be industry-leading accuracy and industry-leading quantity of relevant, actionable information that is produced for the patient or provider, all of which is noninvasive. Lowering the invasiveness barrier allows a solution to one of the main challenges in the realm of prostate cancer screening, which is people do not like the potential risk of false positives using current technology resulting in unnecessary interventions through core biopsy.

Assuming each PSA that's done represents one patient, at best 40% of the population actually bothers with screening. By contrast, 60% of the age-eligible population gets screened for colon cancer and people think that's terrible. Here, it's at best 40%, so 60% of the second biggest killer of men in oncology do not even get screened.

That's basically the approach. We're very sensitive about comparing ourselves to PSA or other technologies because it's all good, right? It's all there to serve the purpose of men empowering themselves with information. Tragically, the PSA is a 40-plus-year-old technology. It was better than the nothing that existed for a long time beforehand, but it's problematic in the sense that it doesn't accurately discern whether there is cancer. It doesn't say you have cancer. It merely says there's a suspicion of cancer, so the patient is pushed to the next step.

European, US, and Canadian studies involving tens of thousands of patients show the false positive rate of PSA is such that well over half, but it's approaching almost 70%, of men who have a biopsy as a result of an elevated PSA come back clean. It's an unnecessary intervention. On the other hand, many men who present with stable or new PSA turn out to have high-risk disease. They're even told to

go home, and they're fine. There's a problem on both ends, but these are the things we're solving.

Are you viewing the test as something to be used in conjunction with PSA or replacing PSA?

Mr. Salman: Replacing PSA would take time. What we're trying to do is replace a reflex PSA number. Our competitors rely on information from the PSA directly, for example, an elevated PSA; however, the concept of what's elevated is arbitrary. Several years ago a PSA of four was bad. Now, National Comprehensive Cancer Network (NCCN) guidelines say a PSA of 2.5 is bad.

It's arbitrary and it's adjusted by age and family history. So what we don't want to do is say, "If you have a PSA of four, then take our test." Our long-term plan is to displace the use of PSA as a tool for measuring suspicion and instead use our test as a tool of definitive screening/detection, but it takes time to get there.

I'm assuming it's a particularly useful tool for men in active surveillance programs, right?

Mr. Salman: Exactly right. Active surveillance suffers from two different challenges right now. It suffers from the incentive system in the US in particular. It's different in Canada and the European Union, but in the US, there is liability on malpractice risk. The failure of active surveillance is bad in the US system. When a urologist is faced with a patient who could benefit from active surveillance, knowing there is a possibility they may fail, they're not applauded for directing these patients into active surveillance. Rather these urologists can be criticized for not having put such a patient into biopsy and definitive treatment right away.

What we're able to do is make it easy and appropriate for patients to be put on active surveillance, because they're classified as very low risk, low risk, or even intermediate risk, and just monitor them every few months with urine. There's nothing invasively being done to the patient. If there is a change, the urologist or their care provider could immediately decide to take them out of surveillance and treat them. Therefore, many more men would benefit from appropriate active surveillance.

> *"What we're trying to do is replace a reflex PSA number."*

The other major challenge is many men are not compliant even with low-risk disease and on active surveillance. They're good candidates for surveillance but don't show up for their next biopsy appointment, which is the standard by which active surveillance is done, because it's a very invasive and unpleasant experience for them. So we solve that problem as well.

In our view, this could be a game-changer for active surveillance. It could be a game-changer for avoiding false positives and reducing unneeded biopsies. It's certainly a game-changer in terms of our much more accurate false-negative approach. We mitigate the false negative rate of current PSA testing. Ironically, PSA portends to a suspicion on the affirmative side that somebody says, "We think you may have prostate cancer by elevated PSA, go get a biopsy." If it's low, they say, "You don't have prostate cancer," so you go home. It's an oxymoron almost. We eliminate that challenge and we certainly believe that we can make a material difference in the engagement with the broader population who right now is choosing PSA testing for a screening strategy.

How would men get tested? Is this a test that you would only get at a urologist's office or could you get it at a general practitioner?

Mr. Salman: We're working to make it available not only at the urologist's office or primary care provider but even at home with a referral. What we're measuring is inherently stable, but we have to work toward that from a clinical validation point of view. We need to demonstrate stability and, as we know, when you give somebody an at-home test, anything that can go wrong, goes wrong. We have to show that if somebody puts it in the freezer instead of the fridge or puts it in the microwave, anything that could go wrong, we've demonstrated enough times that we can account for that.

The goal is wherever the patient is, the patient will be able to provide a urine specimen, send it to our lab, and then they and their providers will be able to get definitively actionable outcome information.

Were your plans for the at-home test accelerated by COVID-19 and shelter-in-place?

Mr. Salman: They were accelerated by that and employers. Employers like Walmart, General Motors, Amazon, and others are making a huge effort right now. They want to reduce their healthcare costs while maintaining good employee/patient outcomes. Their goal is to handle as much of their employees' needs in a primary care environment and for employees who really need to go to specialist care to be able to do so.

We can work with employers to go to a place of employment and have a collection. Employers can also encourage their employees to access our kits and send urine to us as a screening strategy for their age-eligible male employees. This gives them a means by which to reduce poor outcomes and waste, such as costs and lost productivity from their workforce having to go and get biopsy appointments, or seeing a specialist care provider. Lower-income and Black and Hispanic communities oftentimes cannot afford to take that additional day of no pay and go to a clinic to provide a specimen for blood or biopsy. It helps eliminate many of those friction points as well.

What is the cost of the test?

Mr. Salman: We're aiming to make it at least half the cost of biopsy, which averages around $2,500. We're aiming for an initial level of $1,000 to $1,200, then work to optimize a supply chain that has never existed to drive down costs through increased supply. We think we can be more cost-effective in the future.

Is it covered by insurance?

Mr. Salman: It will be. We're working to secure not just Medicare/Medicaid, but private payers. We have validation on utility and economic utility studies being done to support the test both in the US, and other parts of the world. The US and other markets have sophisticated legacy healthcare systems. Other healthcare systems that may not have as many specialists per population or access to MRI machines are open to new ways of doing things. They have what we call the mobile phone versus landline paradigm. Those communities and countries can adopt the next-generation technologies and bypass the entrenched friction of legacy. In the US and other markets, the legacy is the 40-year-old definition, the PSA tests, and what that legacy forces the rest of the system to use. By the way, we do not consider urologists or uro-oncologists to be a challenge or problem. We view them as simply wanting to access the best tools for their patients. We have deep ties to the urology community. We view them as partners and key stakeholders and we're focused primarily on them initially.

Let's say a reader in India reads this. Is there a way he can access the test?

Mr. Salman: We are working to bring this platform globally. One of the ways we want to do so initially is by creating a logistics network where specimens could be collected and sent to labs that we will develop regionally. Our initial plans are two US labs to be commercial this year. We plan on launching labs in Israel, Singapore, Japan, and Europe in 2022.

An Indian patient will be able to send their specimen to one of those other centers. Because it is urine, it's not a biohazard. We're working on that technology; We've already received specimens from Israel and Germany and other markets to test logistics. That's very much part of our goal.

How does a urologist or a family physician offer the test?

Mr. Salman: They order the test and receive a urine collection kit and the portal they can then enter for the patient. They would simply send the urine with a pre-collection system back to our lab and we then process the task. It takes about three days to get a result.

Any other thoughts for men with prostate cancer who may be reading this, either about the test itself or how it fits into the wider array of tools available in the prostate cancer journey?

Mr. Salman: They are first and foremost on our minds. Our goal is to deliver a disease-management solution where they are backed by reliable, accurate decision-making tools at every stage of their disease journey.

We encourage men to take prostate cancer very seriously because those who get tested and have a plan of action for treatment almost always end up being safe, having a good quality of life. Those that do not, unfortunately, can end up contributing to the horrible statistics of the number of deaths from prostate cancer, which is only second to lung cancer in the US.

Our website is miRScientific.com. We hope to be able to share far more information in terms of how they can engage with their care providers to access our tests. We want to be the leading platform to help guide them through the journey to the best possible outcome with the least burden for them and their families. Pp[1]

Patients Speak
My Experience with Genomic Testing

Victor Ortiz spoke with *Prostatepedia* about his prostate cancer journey and experiences with genomic testing.

What was your reaction when you first found out you had prostate cancer? What went through your head?

Victor Ortiz: My diagnosis came after five or six years of experiencing urinary issues while being assured by my primary care physician that it was not important to get a PSA test because of the government guidance against PSA tests at the time. I was getting an annual digital rectal exam (DRE), which I now suspect my primary care physician probably did not know how to do properly.

"I was frightened and shocked at this news. The doctor spent literally less than 10 minutes with me."

The physician didn't encourage PSA measurement even though my father had prostate cancer when he was my current age and there were a lot of other kinds of cancers in my family, including aunts and recently a cousin who ended up being diagnosed BRCA2.

My physician even gave me Flomax (tamsulosin) for urinary problems, which ended up being not at all what I needed. I had some unpleasant side effects. By the time 2017 rolled around, and I was retiring at age 65, I was pretty well convinced that something was going on. I had a strong sense of "knowing".

I went for my annual physical and prostate exam. My GP didn't find anything from the DRE, but my PSA was now going up; it was up around seven or something like that. I insisted—had to insist—on seeing a urologist. She only referred me after a second test, which confirmed two weeks later that my PSA was going up further. She thought the elevated PSA might have been because I'd just been on a cross-country motorcycle ride or it could be an infection. It could be anything.

My reaction at the start was frustration that there seemed to be so much resistance to even getting a urologist to check. When I was finally referred to the urologist, he did a DRE. I asked about a possible MRI to see what was going on if he couldn't feel anything. He said, "Oh, we don't need an MRI to guide a biopsy, you've got a very detectable lump that any competent urologist would feel immediately. I know right where I need to biopsy." So that suggested my primary care physician, who two weeks earlier had given me an exam, was not properly trained in prostate diagnosis.

My first urologist did the biopsy and a couple of days later that particular urologist (who I got rid of very quickly) walked into the exam room and said, "I found it and it's Gleason 8," —I had no idea what "Gleason 8" meant— "... and that's aggressive, but don't worry, I can cure you."

I can cure you? He said those words?

Mr. Ortiz: Those were his exact words, "I can cure you." He said, "We'll take it out, we can do a surgery. Of course, you can look at other options." He said, "You could do hormone therapy or radiation or something, but I don't think you're going to like that. With hormone therapy you're going to be sexually impotent for who knows, maybe two years."

I was frightened and shocked at this news. The doctor spent literally less than 10 minutes with me. I asked what it would take to start scheduling the surgery. He said, "Well, it's going to be a couple of months away." Then he just turned on his heel and left with no particular counseling or sympathy or anything of the sort.

Very quickly after that, I contacted a friend who had prostate cancer and had been going to a support group at University of California San Francisco (UCSF), and said to me, "You really should get in a support group."

I found out that there was a prostate cancer support group in Walnut Creek that was having its monthly meeting the next day. Several group members had just come back from the Prostate Cancer Research Institute conference. They had the new staging manual, which was a life-changer for me.

The group and the staging manual helped me start to understand "Gleason 8," what that finding meant, and how the different treatment options compare. I began to understand what the chances were that I would have to do radiation and hormone therapy anyway, even if I had surgery, and what the side effects would likely be. So, that helped me make a decision.

But, like most people, I was thinking, "Am I going to die?" My father had had a prostatectomy many years ago and had complications. It's a pretty dire thing.

Somebody told me that when you get diagnosed with prostate cancer, you've got a new hobby, which is studying prostate cancer and research as it comes out. That certainly became true.

I felt a mixture of fright and anger, and real resentment at the whole diagnostic process. Then, with the support of my group, I got referred to a different urologist who gave me a pretty thorough exam and spent an hour and 20 minutes with my wife and me going over options and carefully explaining the findings. That sort of concern and attention is what we all need when we are first diagnosed, and I was immensely grateful.

That's a huge difference in approach.

Mr. Ortiz: That second guy, unfortunately, has retired now. It was night and day. Strangely, the first doctor I went to, the first urologist who had such an insensitive approach, turned out is the son of a guy who was my personal physician in Berkeley years ago, who is an absolute prince of a guy. Doctors are all individuals, just like patients, and it is important to find the right ones.

How did genomic testing get on your radar?

Mr. Ortiz: I was concerned about whether I was BRCA positive because of my family history. I had raised that issue with my primary care physician and a couple of others and was told I shouldn't worry about it because my mother had lived to 91. She hadn't had breast cancer, though she had had a large benign tumor in her ovary, but it was not metastatic or anything. She had a huge surgery when she was about eighty years old and, amazingly, survived it. There was no concern whether my father's side of the family had it.

My first course of treatment, my primary treatment, was only four months of androgen deprivation therapy (ADT), high-dose rate (HDR) brachytherapy, and then five weeks of intensity-modulated radiation therapy (IMRT).

The theory was, "Let's see if this works. It works on 70 to 80% of patients with a similar diagnosis, and they don't have recurrence, and it's very likely you will do well." My doctor at the time said there was not very good evidence of an increase in survival if you extended ADT after radiation. It just gave you all kinds of side effects for 18 months and really didn't have much benefit.

We did a short course. Soon after that, as my testosterone began to come back, my PSA started leaping up dramatically. At that point, I was comparing myself to other people in my prostate support groups. I was concerned that my PSA seemed to be going up much faster, and I began to suspect that I had something else going on that made my cancer more aggressive.

And so, I went for an Axumin scan and they didn't find anything. My PSA was going from four to six to eight to nine. I ended up going down to UCLA for a PSMA PET scan. They found a met in my L3, and a little bit of illumination around the prostate bed, but that could all be residual normal tissue after the primary radiation as it hadn't been even a year since my primary treatment.

I insisted at that point that I get genomic testing. We were talking about it in the prostate support groups at the Prostate Cancer Community. People there had the importance of knowing about possible genetic mutations on their radar screens.

You were the one who asked?

Mr. Ortiz: I was the one who suggested I needed it. I got the prescription for the COLOR diagnostic kit. I did a couple of cheek swabs with that and they never worked. I was going months without results. Finally, I got a blood test which was sent in. I had to go over to UCSF and it took a fair amount of work to finally get a result. And then they came back and said, "Yeah, you're BRCA2 positive."

Had we done the genetic testing earlier, I think it's quite clear that the attitude might have been different about my rapidly rising PSA. It might have been taken more seriously.

Do you wish you had gotten the testing earlier? Would you recommend other men do it earlier?

Mr. Ortiz: Absolutely. I wish I'd done it earlier. Especially given my family history and my symptoms.

I guess added information is always useful. If you don't end up using it, you don't end up using it.

Mr. Ortiz: Right. And if you have PSA that's rising abnormally fast after primary treatment, you may hear, "Well, it could be just a testosterone boost." But in my reading about it, almost no one has a testosterone boost the way I was having it, with no leveling off and subsequent decline.

The key thing in all of this is that no one was doing comprehensive treatment management for me. No one was advocating for me. I was doing all of that. I was managing treatment, being my own advocate, and fighting like hell every step of the way to get treatment.

What happened after you tested positive for BRCA2?

Mr. Ortiz: When I finally got the results, UCSF immediately referred me to a genomic counseling session. They have a whole program for dealing with genetic issues with all kinds of cancers. I met with one of the docs there, who works very closely with my medical oncologist, so they're pretty much on the same page as far as the effects of BRCA2 and prostate cancer. We began to discuss whether PARP inhibitor treatment, or something like that, was in the cards for me, and when and how.

The information I've gotten so far is that research has shown no particular known overall survival advantage for using PARP inhibitors early, and they have side effects such as fatigue, and other things that probably don't provide any advantage to doing treatment with PARP inhibitors this early in my treatment progression.

The thought right now is it may be something that can help later in my disease progression. Right now, I'm still responsive to ADT. I'm on a break right now from the ADT, and my testosterone and my PSA are beginning to rise.

I had a meeting with my MedOnc doc yesterday The current plan is that if and when my PSA gets up to around one or two — it's 0.109 right now — then we'll do another PSMA scan. It might be that if I have only a few mets or one met or something we can zap it with stereotactic body radiation therapy (SBRT), and hold off on ADT. I do have some heart issues, cholesterol, and so on. And my dad died of a heart attack; there's a lot of heart attacks in my family on both sides.

I want to avoid Lupron (leuprolide) and Zytiga (abiraterone) as long as possible again. That's the plan: watch and see how things go, how fast it goes up. Hopefully, I'm still responsive to ADT, and if my mets are not so widely spread that we can't use radiation, I can make some new ADT treatment choices then. Certainly, the trend right now is to use SBRT much more widely and on more mets than it used to be.

That's kind of the prognosis at this point, no particular genetic-related treatment in the plan until I get a castrate-resistant diagnosis, and we're starting to run out of other treatments. Right now, as I understand it, the PARP inhibitors give people six to 12 months more overall survival generally, but the cancer comes popping right back after that. We'll see what happens with the research in that area. That's the most current information I have at the moment.

Tell me more about your support community.

Mr. Ortiz: I had a friend who was involved in the UCSF cancer support community, and he suggested that I look for one. I just googled cancer support groups and Cancer Support Community came up. It turned out they were in Walnut Creek and had a meeting the next day.

That was just dumb luck on my part. Cancer Support Community, which is a national network, turned out to be a wonderful group. They do all kinds of cancer support, and all kinds of different counseling, exercise groups, nutritional groups. They do a bunch of what they call resource groups, which are cancer-specific, like the ones that we do for prostate cancer. And those are more focused on helping people make treatment decisions and keep up with research and so on, but they do also deal with some level of psychosocial issues.

> *"I felt a mixture of fright and anger, and real resentment at the whole diagnostic process."*

And then there are what they call participant groups, which are for cancer patients. Those are almost entirely psychosocial. They also have caregiver support groups for the family members. They have children's groups and groups for parents of children with cancer and just a wide range of stuff. Their mission is basically that no one should have to face cancer alone.

That's a simple but powerful message.

Mr. Ortiz: Very powerful. They say they want all people to be empowered by knowledge, strengthened by action, and sustained by community, which I love. It's one of the best "Mission, Vision, Guiding Principles" statements that I've ever read. And as a consultant, I've helped people write them for years. They're not easy to write. I joined and there were two prostate groups, one was for localized and the other was for metastatic. I joined initially in the localized group because that's what we thought I had. And there was a fair amount of fear. Nobody wanted to go into the metastatic group for obvious reasons. We thought it was the doom-and-gloom group. Though many of the people who attended were more senior members in the localized group and actually were metastatic. They were kind of our research mavens.

We had experts who have been around, who've had cancer for many years, who would come to the localized group and really help people with their staging decisions and understanding all the medical data, and so on. I started in that group.

When I got diagnosed as metastatic, I joined the metastatic group and found that it was absolutely wonderful. The people were kind and supportive. They were focused more on treatment options. One of the things I helped encourage was dealing with the psychosocial issues because, at that point, I was really overwhelmed with the amount of energy and effort it had taken to finally get diagnosed when I'd known for months that something was wrong. I had just known inside that something was going wrong.

When you know, you know. You get a feeling.

Mr. Ortiz: You get a feeling. And I remember really breaking down. That was the first group that I could really let go and talk about what I considered emotional armoring that I had had to do in order to stay focused and fight through the system, and not give up and not get depressed.

The group helped me stage initially and then helped me work through the issues of being metastatic. It was hugely important. The guy who was running it had helped form the Cancer Support Community 30 years ago. He was a PhD psychologist. Late last summer, he turned 80 and decided he might retire so he could go do other kinds of therapy somewhere else.

Cancer Support Community had grown, it was less of a family and more of a real enterprise at this point. The man who started the group had the initial pioneering spirit of it. He asked me if I would be interested in facilitating the prostate group because I have a degree in psychology. And so, I've become a part-time employee of the Cancer Support Community as well. I know more about their types of groups. I'm now the facilitator for that group. I don't have a license in psychology; I did a lot of consulting with my psychology degree rather than therapy. But I can be a therapeutic facilitator for the prostate groups. I'm just working a few hours a month.

I assume everything is virtual now?

Mr. Ortiz: Exactly.

I've been talking to a lot of group participants who say the virtual programming is nice because it allows people who couldn't make in-person meetings for various reasons to attend. Going forward, do you think you will incorporate virtual programming into your plans, even when you can meet in person?

Mr. Ortiz: We will. We'll have some groups that will be virtual continuing for exactly those reasons. There are virtues of the in-person meeting, of course. We haven't figured that out yet. It's too early and we don't know how much money that will take and so on. But we'll definitely keep virtual stuff going on.

Any last thoughts for men reading this?

Mr. Ortiz: Certainly. We are encouraging men to get genetic testing under a number of circumstances when they are newly diagnosed. If they have any sign of cancer in the family, they might as well know, and their children should know. I have one brother and I have one son. Both of them were tested using the COLOR system and thank goodness both of them came out negative.

That was a huge relief for me. That's one of the other things when you do find out that you have a genetic situation, the idea that you've passed this along to your children is just a horrifying thing to ponder.

The main thing is: If you have any kind of history, it won't hurt to check. It's good to know. And if you do know you have a genetic condition, then the chances are that people will take you more seriously when your PSA does something abnormal or if there are any other kinds of complications.

Clearly, there are different treatments if you do have a mutation than if you don't. And research continues to be done in those areas. It's one more area of research you need to track.

When I first got diagnosed, I made the decision that I was going to be completely transparent about my experience. I started publishing my treatment history and pictures of what I was going through

with HDRT and all of that on my Facebook page. I encouraged any men that I knew or anyone who read it (or anybody who knew a man who might have it) to get into a support group and be proactive.

"We are encouraging men to get genetic testing under a number of circumstances when they are newly diagnosed."

And the support group community is an important source of information.

Mr. Ortiz: Yes, because then you're in with a whole bunch of other people who are reading things you're not reading and attending workshops you can't attend. The emotional support and the encouragement to be assertive and to be proactive in your own treatment are immensely helpful, I think.

One of the things men suffer with is isolation and wondering: "Is it only me?". When I've got a concern, it's difficult to assess m I blowing it out of proportion, or is this legitimate? Your doctors only have so much time and they only have a certain perspective by their specialty. Being with a group of people who have all kinds of conditions and all kinds of experiences is immensely helpful. Pp[1]

Before you take this route...

Prostate Biopsy

ExoDx

TAKE THIS ONE.

Discover the ExoDx™ Prostate Test to assess a man's risk for clinically significant prostate cancer.

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The ExoDx™ Prostate Test.
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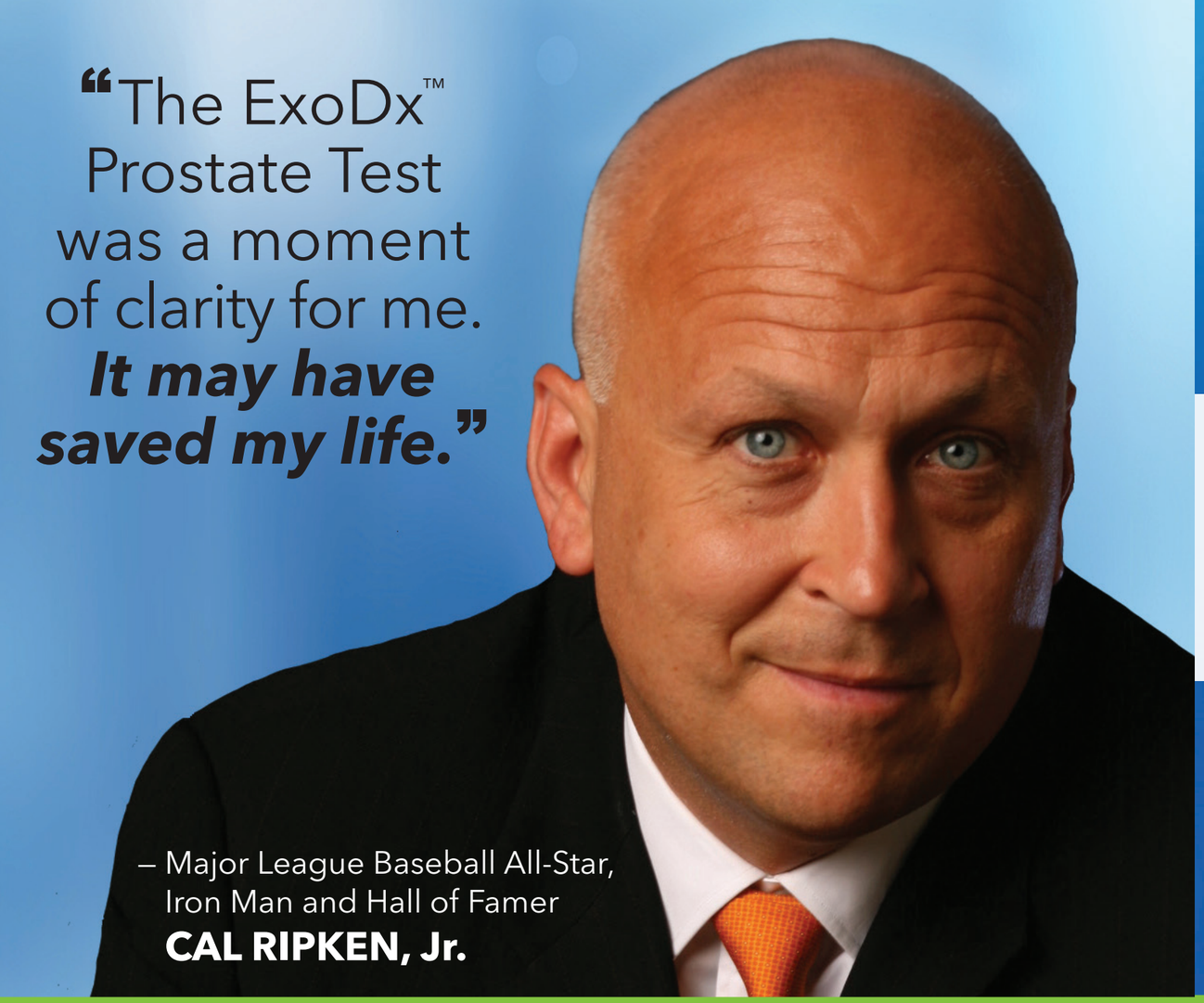
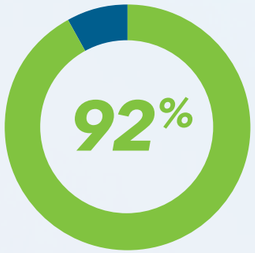


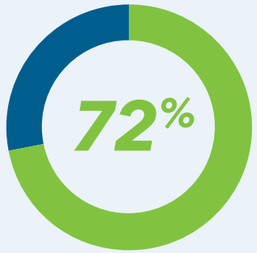
“The ExoDx™ Prostate Test was a moment of clarity for me. ***It may have saved my life.”***

– Major League Baseball All-Star, Iron Man and Hall of Famer
CAL RIPKEN, Jr.

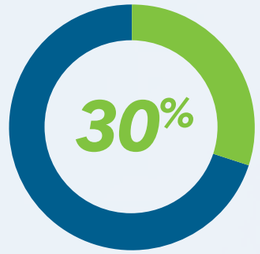
ExoDx Prostate Test (*EPI*) use resulted in a significant increase in patient compliance with physician biopsy recommendations, and demonstrated the following key points:



of patients complied to physician recommendation to defer biopsy due to The EPI Test based on the physician-patient shared decision



of patients complied to physician recommendation to proceed to biopsy due to The EPI Test based on the physician-patient shared decision making, compared to only 39% in the SOC control arm



more cases of clinically significant or high-grade prostate cancer were detected by physicians due to increased compliance, compared to the standard of care control arm

The ExoDx™ Prostate Test helped Cal Ripken, Jr.
See if the test is right for your patients.

LEARN HOW TO FIGHT LIKE CAL.

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Prostate Cancer is Manageable

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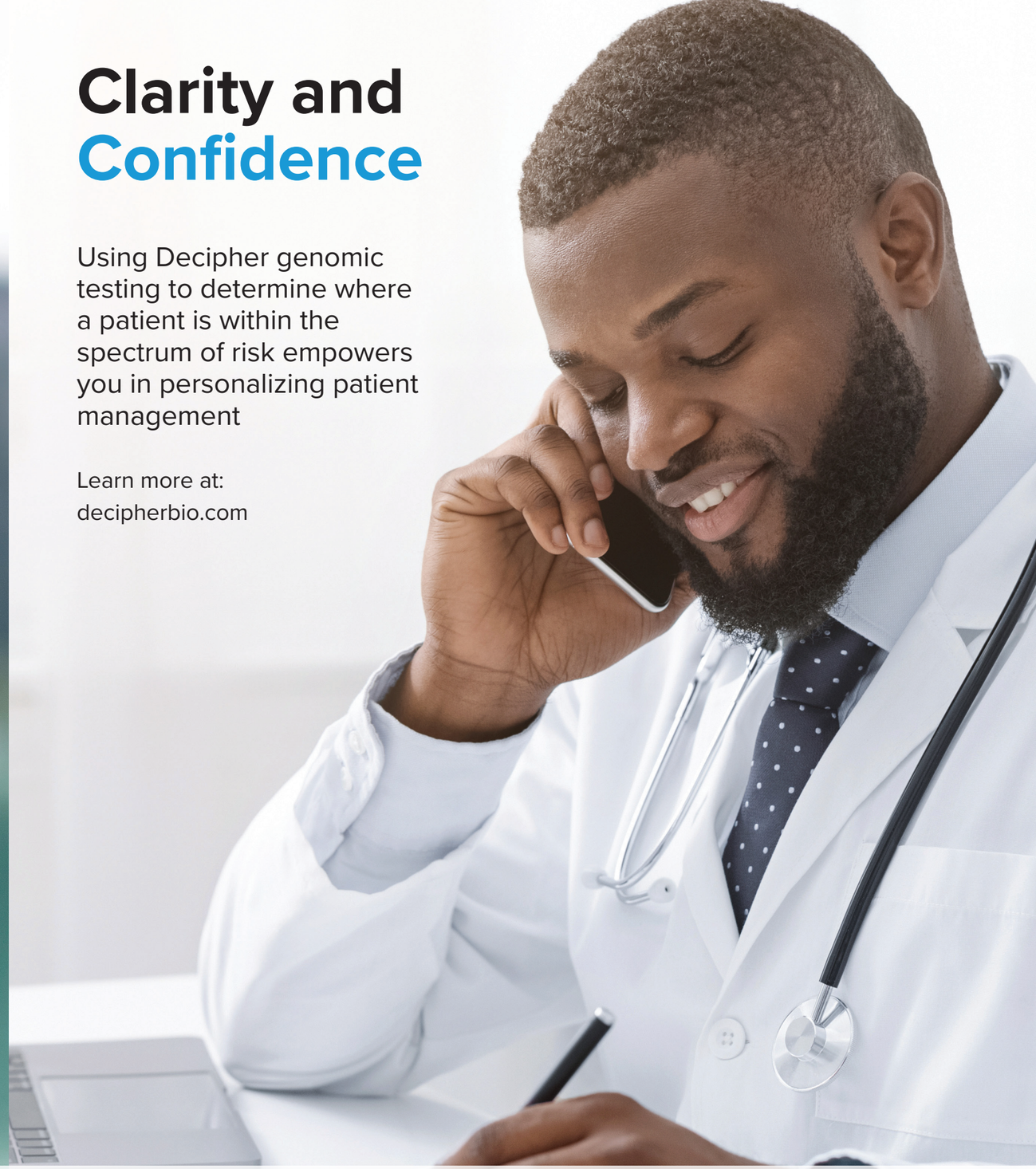

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