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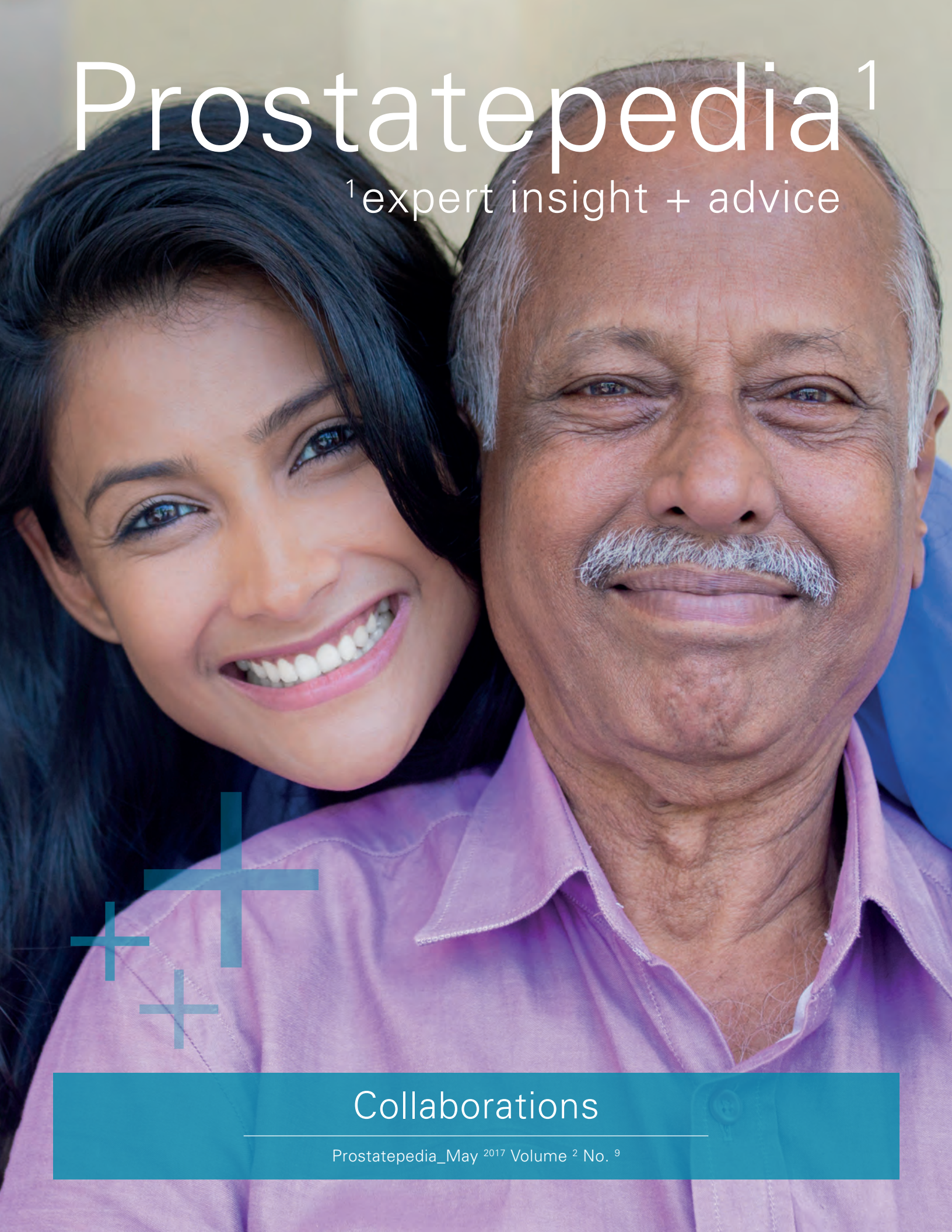

Collaborations

Prostatepedia_May [2017] Volume [2] No. [9]

In this issue....

This month, we're delving into large cooperative group efforts in cancer research. A key factor driving these collaborations is the power of *big data*.

Today, the term *big data* is used to describe information on the scale of petabytes. How much is a petabytes? A large hard disk on a personal computer can store a terabyte. A petabytes is 1,000 times larger.

A few years ago, I attended a meeting on the Cancer Genome Atlas. (The Cancer Genome Atlas was an attempt to collect information on the gene, RNA, and protein expression patterns of major human malignancies.) They were collecting 15 petabytes of data a day. Clearly, just storing that amount of information in a manner that can be retrieved and analyzed is a technical challenge. But the task of understanding cancer biology requires information on this scale.

Why even try to do this for cancer? We know that cancer cells' behavior is determined by a complex array of molecular changes. We hope that if we understand what drives a man's prostate cancer, we might gain insight into how best to kill his cancer—or at least block its growth.

How do we go about examining data on this scale? Fortunately for those involved in bioinformatics, others have already addressed these issues. Google, Facebook, Amazon, and other technology leaders have spent years studying Internet information at this —and larger—scale. These tech leaders have made many of their insights and tools publically available.

One of the most promising approaches to analyzing complex information is to use computer programs that can learn, or *machine learning*. As a result, companies like Google, Amazon, Facebook, and Microsoft have major programs aimed at improving machine learning.

One particularly successful approach to machine learning is based on deep neural networks. The Google subsidiary Deep Mind has developed deep neural networks that can defeat the best human players at the game Go. Go is too complex for even the most powerful computer to analyze the consequence of every step. Instead, the computer program must develop an analog of human intuition. These deep neural network programs deal with a level of complexity that approaches the scale we encounter when we attempt to understand cancer cell biology.

What steps do we need to take to understand prostate cancer biology? First, we need to collect detailed information about the molecular changes that determine this cancer's biology. This month's conversations feature individuals and organizations either actively collecting and analyzing this data, or funding the efforts.

Charles E. Myers, Jr., MD

Contents:

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www.prostatepedia.net

ISSN: 2381-4020

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Prostatepedia is published in Charlottesville, Virginia by Rivanna Health Publications, Inc.

James C. Costello, PhD
Crowdsourcing Better Predictive Models

Dr. James Costello led an open-data, crowdsourced challenge to better predict survival in men with metastatic castration-resistant prostate cancer (mCRPC).

Prostatepedia spoke with him recently about the challenge, what his group found, and the intersection of big data and cancer research.

How did you come to focus on computational oncology?

Dr. Costello: I have a diverse background, mostly focused in computational sciences.

I got my PhD from Indiana University in Informatics, where I was doing fruit fly (Drosophila) research. I was looking to address questions around data integration to see if we could predict function for proteins with unknown function. I was then going through and experimentally validating those functions.

This was before the big data revolution, but there have always been questions about data integration. How do we make sense of the data that is out there? How do we bring it together? What is the most effective way to leverage this data to gain biological insight or generate hypotheses?

That skillset brought me to Dr. James Collins's lab, now at the Massachusetts Institute of Technology. His lab focuses on questions in synthetic biology and systems biology. My skillset complimented the questions they were looking at, like how can we leverage the large amount of gene transcriptional data to identify mechanisms of antibiotic resistance in bacteria?

I went from fruit fly (Drosophila) research to antibiotic research. Around the same time, I had an opportunity to work with Dr. Lynda Chin's lab when she was at the Dana Farber Cancer Institute.

In her lab, I helped to develop methods for looking at drug combination prediction using gene expression data in melanoma. They had some really great data. We worked on a collaboration that identified a drug combination currently in clinical trials for treating NRAS-mutant melanoma.

I've wandered, but I've always focused on using computational methods to make sense of data, which led me to my current job: Assistant Professor in the Department of Pharmacology at University of Colorado, Anschutz.

My current focus is on how we make sense of all of the cell line and tumor –omic data we're generating within cancer biology, of the mechanisms of action, and the molecular sub-types. How we can better treat patients with drugs and better identify which patients will and will not respond to specific drugs?

Can you speak a bit about this concept of crowdsourcing cancer research?

Dr. Costello: Dr. Charles Hughes-Jones, then VP of Medical Affairs at Sanofi Oncology, started to ask questions about how they could share the clinical trial data generated by pharmaceutical companies and academic research institutions.

Typically, a company runs a trial and then the data goes into storage where it just sits. He asked, from a pharmaceutical perspective: Can we better leverage all academic and pharmaceutical clinical trial data? Can we learn from that data how to make better clinical trial design decisions? Can we learn from larger patient cohorts how patients respond to different drugs? Can we bring drugs to market more quickly based on insights from data we have stored in databases that nobody now has access to?

Project Data Sphere (https://www.projectdatasphere.org) began to address those questions. The motivation

behind Project Data Sphere has been to make clinical trial data open and accessible to any researcher anywhere in the world so they can better identify mechanisms of drug response, better characterize patient response, and better understand how to bring drugs to market faster.

Their goal is to build an open access digital library of clinical trial datasets and then give researchers access to it. With clinical trial data, there are issues with privacy and legal implications of the data, so one of Project Datasphere's big efforts has been to come up with data governance guidelines, a data structuring collaborative agreement, that different institutions can sign onto, provide de-identified data, and allow people to mine these data.

The initial goal was to bring together comparator or control arms of clinical trials. That is important because pharmaceutical companies typically don't want to give priority results for whatever drug they're developing. But the comparator arm is the group of patients given standard of care treatment or a placebo. The data from the comparator arm is still very valuable. These are patients being treated with the standard-of-care. If we can pull information from multiple independent trials, we can collect the number of patients needed to statistically address questions that are deeper than simply determining if the treatment is performing better than the standard of care. For example, how do the clinical and genomic patient measurements predict response to standard of care? Can we identify patients that might be discontinued from treatment due to adverse events?

Now that we have data available, the idea of crowdsourcing is to open up this data along with a set of well-defined questions, and ask anyone who wants to address the question to do so. Project Data Sphere partnered with DREAM (http://dreamchallenges.org/) and Sage Bionetworks (http://sagebase.org/) to run the Prostate Cancer DREAM Challenge, an effort to bring communities of researchers together to address key questions in the prostate research field. While the focus here is prostate cancer, DREAM has run many other cancer Challenges, with a focus on building predictive models.

"It could be anyone: a doctor, a computer scientist, or a high school kid in India… That is powerful."

For the Prostate Cancer DREAM Challenge, there were a few questions we were interested in asking, one of which was, "Can we build a better prognostic calculator for metastatic castration-resistant prostate cancer (mCRPC) patients?" The other was, "Can we predict which patients will discontinue treatment due to adverse effects of the drug treatment?"

Regarding the first question, we can gain insights into the development of disease and response to treatments by studying cohorts of patients that have been similarly treated. Understanding what clinical measures are predictive of overall survival allows the doctor to assess these measures when making treatment decisions. Prognostic calculators capture this information in a statistically reliable and robust model, thus capturing this information in the best model possible was a high priority for the Challenge.

For the other question, we were interested in asking if a model could be developed to predict the likelihood that a patient will have an adverse side effect of their treatment and subsequently have to discontinue treatment. Often, a patient treated with standard of care will have adverse effects. Knowing which patients will have severe responses leading them to discontinue the drug is an important question.

This is where the scale of data becomes very important. Roughly 10-20% of patients will discontinue treatment because of adverse effects. This is a very small proportion of patients in any single clinical trial. In order for us to gain the statistical power to identify patterns of treatment discontinuation, we need to sample data from multiple independent trials.

Since the data has been compiled by Project Data Sphere, we can ask for the first time which clinical features of a patient allow us to predict if he will discontinue a drug because of an adverse side effect. This is another tool a clinician can use. If a patient has a high likelihood of experiencing one of these adverse side effects, the doctor can still give standard of care while also thinking about closer monitoring or potentially other treatment options.

How do the DREAM Challenges work?

Dr. Costello: DREAM Challenges are one set of many community-based, open-data, crowd-sourced challenges. DREAM stands for Dialogue for Reverse Engineering Assessment and Methodology.

Originally, two New York professors named Dr. Andrea Califano of Colombia

University and Dr. Gustavo Stolovitzky of IBM, were very interested in the question of network inference and how to take large numbers of transcriptional data and let the data determine which genes are functionally connected. Can we evaluate the performance of the computational methods that do this in a robust manner?

That idea has evolved over the years beyond network inference and gained a lot of traction. It has moved into questions about biomedical and general systems biology—for example, the Prostate Cancer Challenge.

If we have important questions and really good data, then we can open the data to the community, propose the question, and anyone interested can attempt to solve this question. It could be anyone: a doctor, a computer scientist, or a high school kid in India or any other country. It doesn't really matter. Anyone could propose whatever solution they want and it will be evaluated. Importantly, the solutions are evaluated on a held-out, gold standard dataset that is unpublished and not publically available.

Today, you hear a lot about reproducibility in science. One of the key challenges in any study is that the developer of the method has the data *and* the methodology. The researcher is the judge, jury, and executioner of the entire process.

If we take the final performance evaluation out of the hands of the model developers, we can provide an unbiased assessment of how the methodology does in relation to the held-out, gold standard dataset.

The framework of the DREAM Challenges allows us to focus a large community of researchers on one specific question. In the Prostate Cancer DREAM Challenge, a total of 50 teams comprised of 200 researchers from around the world were focused on addressing the two previously mentioned questions within a five-month period. That is powerful.

After the Challenge is complete, and after we have identified the top performing teams, we run a post-Challenge phase where we ask if we can improve on the best performer by taking an aggregation of the community. If we look at the solutions from all 50 teams in the Prostate Cancer DREAM Challenge, we can learn insights about the data and the methods that can produce a better prediction than any individual team.

We've seen consistently that when we take the aggregation of the community, we can almost always find a better, more robust, solution to a problem. But this only works if you have a lot of teams working on the same Challenge—the same data, the same question.

The DREAM Challenge structure has another benefit. If we have 50 independent teams working on the same challenge and one team comes up with a solution that a certain clinical feature is predictive, we might trust it or we might not, depending on who is on the team and how good the statistics are. But if 45 of the 50 teams, independent of each other, come up with the same or similar solutions we have a strong confidence that the clinical feature really is predictive.

Why only 50 teams? Why not 200? Or more?

Dr. Costello: We're open to whoever wants to participate, whoever wants to join. The number of teams varies from Challenge to Challenge; we can gain new teams based on incentives. For example, we are currently running the Digital Mammography DREAM Challenge (https://www.synapse.org/Digital_Mammography_DREAM_Challenge) in partnership with the Laura and John Arnold Foundation (http://www.arnoldfoundation.org/), Coding4Cancer, and the White House Office of Science and Technology Policy. This Challenge looks to improve the predictive accuracy of digital mammography in identifying breast cancer.

There are a million dollars worth of prizes associated with the Challenge, so as you might imagine, more people are participating. Typically, the Challenges are academic efforts: incentives include publication and potentially developing a model that will become standard in the field.

In the Prostate Cancer Challenge, about 600 people registered and accessed the data with 50 active teams of around 200 individuals.

We try to recruit smart people from different fields to work on these problems. There are a lot of bright engineers, physicists, and computer scientists who might not know what it means to build a prognostic model in prostate cancer, but if we give them the data, the question, and the general framework for what they need to do, they may say there's a really cool idea we use in physics all the time. What if I apply that idea to this question and see if it offers any more predictive power? Or an engineer can say, here's a methodology I use all the time that might fit this question. Let me apply it and see what happens.

Can you talk a bit about the results from the Prostate Cancer Dream Challenge?

Dr. Costello: We were able to identify a predictive model that is better than

the currently standard reference model in the field. Based on a patient's clinical features, the top-performing model can better predict if he will or will not respond to therapy. That allows doctors to make decisions on a more statistically accurate level.

In addition, we were able to validate some previously identified clinical features, which adds confidence that these features have predictive power. Several of the top performing teams found other interesting predictive features that had not previously been identified.

The top performing team—a group from Finland led by Dr. Tero Aittokallio—had a novel approach. They looked at interactions between different features. Typically what a doctor would do is take a set of single features from a patient, enter them into a calculator, and get some statistical prediction.

The Finnish team looked at how these individual features interact to give predictive value. With that, we were able to disentangle some of the correlations seen between the variables. We can actually explain some of these predictive single features by the way that they interact with, for example, blood measurements.

In that context, it gave us some insight into how clinical features combine to provide predictive power. This means we can gain some insight into the underlying biology of prostate cancer.

What problems do the other Challenges address?

Dr. Costello: We're going to be rolling out one on multiple myeloma. There was one in breast cancer a few years ago. Others focused on basic science like how transcription factors bind to the genome and if we can predict where these transcription factors bind based on sequence and other –omics measurements?

There is a lot of genomic data being generated today from next generation sequencing of tumors and normal sample. How do we correctly identify the somatic mutations that occur? How do we effectively identify mutations? We need to effectively characterize tissue heterogeneity within tumors. Can we use RNA sequencing data to identify these aspects of tumors? There is a series of Challenges around those questions.

There are also Challenges that ask questions about drug sensitivity prediction and drug combination prediction. AstraZeneca recently supplied data for a Challenge on drug combination prediction. Questions in that Challenge revolved around effectively predicting combinations of drugs based on single profiles, combination profiles, and genetic features of the cell lines that they were using.

Current, future, and archived Challenges, along with the methods that solved the challenges, the data and the documentation can be found on the DREAM website: http://dreamchallenges.org/

You depend on pharmaceutical companies to provide data?

Dr. Costello: Yes, and no. Pharmaceutical companies are producing some of the really big datasets, but up until recently, most of the efforts have leveraged data generated by academic institutions.

A lot of the early Challenges on network inference were based on publicly available data. Government agencies, like the Department of Defense and National Cancer Institute have participated. We've collaborated with a variety of different institutions.

We're now partnering with bigger pharmaceutical companies simply because they have a ton of data. They have a lot of questions and want to move more quickly.

With efforts like the Cancer Moonshot, part of the 21st Century Cures Act, there has been a really big emphasis on data sharing and on working together to solve problems. I think we'll see more and more buy-in to open-data from pharmaceutical companies.

Do I think Challenges are going to be the solution to cancer? No. But I think this is another paradigm or research modality that will be very important in moving big data questions in cancer research forward in the future.

I don't think that anybody will tell you that the amount of data we're generating is going to slow down in the near future. We really need to think about how we address the challenges big data presents. This will be one approach in a set of approaches. Data sharing and collaborating will move things along more quickly.

If we can collaborate and focus 50+ teams on the same question within a very short period of time, we can get to a solution much faster.

We're still in the nascent stages of the precision medicine field. It will be slow going if we follow the old way of doing science: focused on one thing at a time. Working together and thinking about how to address these bigger questions will be key moving forward. Pp1

Justin Guinney, PhD
Crowdsourcing Cancer Research

Dr. Justin Guinney, of Sage Bionetworks (http://sagebase.org/), talks about crowdsourcing cancer research and how it can translate into better patient care.

What path led you to Sage Bionetworks?

Dr. Guinney: I'm the Director of Computational Oncology at Sage Bionetworks. I lead Sage's cancer research efforts. Cancer is not the only thing we do here, but it's certainly one of our major research areas.

I was in the tech industry for a number of years. I was an entrepreneur in Chicago before I had the opportunity to leave what I was doing and think about what lay in my future. In a very fortuitous way, I learned about computational biology.

Back in 2005, computational biology and bioinformatics was a nascent field. The concept of data-driven biomedical research was—and still is—a work in progress. I wanted to see if I could utilize the skills I developed in the tech field.

I pursued a PhD in Computational Biology at Duke University. It was among just a handful of programs offered nationally at the time. While I was at Duke, I quickly got involved in cancer genomics.

> *"Groups didn't readily talk to each other or share data..."*

When I graduted, Sage had just formed. It was an outgrowth of Rosetta Informatics, which was owned by Merck at the time. A group led by Dr. Stephen Friend left Merck to form Sage. I was the first non-Merck, non-Rosetta employee at Sage.

I joined in 2009 and then became the Director of Cancer Research in 2014.

Can you give us a big picture view of Sage Bionetworks?

Dr. Guinney: Sage is colored by the intentions of its founder, Dr. Stephen Friend, who recognized that biomedical research was operating in silos. Groups didn't readily talk to each other or share data.

Even though collaboration has always been a pillar of biomedical research, buried within that is this reluctance to share widely, to make data that is perhaps paid for by the public taxpayer a part of the public domain. There was this idea that if you could tear down these walls, or at least make them more permeable, than you could accelerate the pace of research. You could refocus the intention of research back onto the patient rather than on tenure.

That is how Sage started. Our goal was to lead by example and to experiment with different forms of collaboration. The DREAM challenge is one of those experiments that has blossomed and done quite well as a form of collaboration and research acceleration.

What are your DREAM Challenges?

Dr. Guinney: The Challenges are crowd-sourced competitions. We find an appropriate and interesting scientific question that can also be approached in a quantitative way. There are several ingredients to a Challenge. We need an interesting scientific question. We need datasets that can be shared and studied. We need a community interested in supporting and participating in the development of models and utilization of data to answer that question.

What kinds of Challenges have you issued?

Dr. Guinney: DREAM (http://dreamchallenges.org/) started

in 2005. It focused on a particular set of questions in the computational biology space using the idea of network reverse engineering—trying to describe and model gene or protein interactions and then infer associations using different types of data.

DREAM has since expanded outwards to at a broader set of biomedically related questions. We've run a variety of Challenges over the years.

The Prostate Cancer Challenge asked a clinically-focused question using Phase III clinical trial data. There was no molecular data, which tends to characterize many of our other Challenges, and focused on the use of the lab and clinical data to improve models of prognosis in men with metastatic castrate-resistant prostate cancer.

Originally, DREAM was operated out of Columbia University and IBM. Today, Sage manages the operations of DREAM, along with a team of directors at multiple institutions.

The first Challenge Sage was involved with focused on breast cancer prognosis and developing models to differentiate women at high or low risk for breast cancer. That Challenge used data from a variety of sources, including mRNA genomic data, copy number data, and clinical traits.

Since then, there have been a number of other Challenges, such as prediction of drug sensitivity in a large cell-line panel using genomic data; calling of somatic variants using genomic DNA; and the study of tumor heterogeneity and clonality in tumors.

We are currently running a challenge called the Digital Mammography Challenge. We're looking at how we can use machine learning techniques

"The Prostate Cancer Challenge asked a clinically-focused question."

–applied to digital mammography screening images – to improve the detection of women with cancer.

Where does the data in your datasets come from?

Dr. Guinney: From a variety of sources. It ultimately depends on who is proposing the Challenge, and the partners involved.

Some Challenges are external. DREAM now has a reputation: groups will approach us and say, "We have this great idea," or "We have this great dataset, and we'd like to run a DREAM challenge around it." That is increasing.

For example, a Challenge that we're preparing to launch looks at identifying individuals at high-risk for multiple myeloma.

Celgene (https://www.celgene.com/), a company that specializes in multiple myeloma, is very interested in this question and is working with Sage to host this Challenge. We have subsequently reached out to multiple groups who study MM and have access to relevant data, and asked if they they were interested in collaborating.

AstraZeneca is another example. AztraZeneca routinely runs drug sensitivity screens on cell lines using their compounds. Recent interest has been in understanding combination therapies—looking at how two compounds when applied simultaneously to a cell line impacts its viability. They've done this across many different compounds and many different cell lines.

At the end of the day, the question is, "What can you actually do with this data to learn about the rules of drug synergy?" By opening their data up to the Challenge community, AstraZeneca was hoping that innovative approaches would emerge that would illuminate how genetics and genomics can be used to predict combination therapy and drug synergy.

Those are two examples of how datasets came to us and allowed us to craft a Challenge question around them.

Is there anything else you'd like to add about the promise of the Challenges?

Dr. Guinney: People often ask, "What is the impact of these Challenges? Is there a clear line between the Challenge and a clinical impact or breakthrough.

In general, biomedical research is incremental and not about *breakthroughs*. Sage and DREAM bring innovation to the biomedical space by engaging many diverse communities. These communities may straddle different spheres. We bring innovation through our ability to reach individuals and labs who bring orthogonal thinking to a particular problem.

We also bring a rigor to the field that is often lagging. There is this idea that people who develop a method are always going to be biased in their assessment of their method. They're always going to say, "My method is better than other methods."

How do you design a framework that can objectively assess the differences between diffrent methods? As we become more quantitative and computational in nature, we can ask these questions. We can say, "Let's rigorously assess methods using very well-defined quantitative metrics."

"There will not be any one approach to the cure for cancer."

By structuring these Challenges the way we do, we can develop very solid benchmarks and say: "This is the state-of-the art. Here are the methods and approaches that are the most promising and that we have assessed in the most unbiased way possible."

Does this represent a new way of thinking about how we approach cancer research?

Dr. Guinney: There will not be any one approach to the cure for cancer. It will require many people doing many different types of research. We're expanding the diversity of approaches.

We provide something that has been missing: rigorous assessment, especially as the biomedical space becomes more quantitative.

Data generation is not a problem these days. In fact, we're increasingly recognizing that the biomedical field is overwhelmed with data.

Now that we're a data-rich science, how do we translate that data into real findings? We're going to do that by recruiting data scientists who bring innovative and creative ways of approaching analysis, as well as methods of rigorous assessment. Pp

Mark Buzza, PhD MBA
Funding Global Collaborations

Dr. Mark Buzza, the Director of Movember's (https://us.movember.com/) Global Biomedical Research Programs, is one of the driving forces behind the organization's international collaborative approach and an evangelist for accelerating patient outcomes through global collaborations.

Prostatepedia spoke with him recently about Movember's approach to funding global research consortiums.

How did you come to work for Movember?

Dr. Buzza: I did a PhD in Molecular Medicine at the University of Melbourne. Straightaway, I decided I wanted to move into industry. I ran global Phase III clinical trials in the pharmaceutical sector—cardiovascular disease, diabetes, and central nervous system trials—and then wanted to move into biotech.

I went back to school to get my MBA and moved into the biotech arena. I was the Development Manager for a small publicly listed biotech company developing HIV and oncology immunotherapeutic vaccines. After that, I went into management consulting and then went on to work at the Australian Red Cross Blood Service running a large strategic national program focused on optimizing the plasma supply chain to benefit patients with a range of immune, neurological, and hematological disorders.

"Our vision is to change the face of men's health."

Still, I wanted to bring all my different skillsets together. I came across the Movember opportunity in 2011 and fell in love with the concept of developing global collaboration models, of bringing the global research community together to improve outcomes for patients.

Six years ago, I joined Movember to run the $5 million GAP1 biomarker initiative in prostate cancer. Last year, I was promoted to the Director of Global Biomedical Research Programs, which means I oversee Movember's $265 million investment across all of our biomedical research partners like Prostate Cancer Foundation, Prostate Cancer Canada, Prostate Cancer UK and other national investments and partnerships, as well as Movember's Global Action Plan. I'm extremely fortunate to lead a highly experienced and dedicated team equally as passionate about changing the face of men's health.

Everybody knows about Movember's annual moustache fundraising campaign, but I think few people know what you actually do with the money. Can you talk a bit about the research you fund?

Dr. Buzza: Movember started back in 2003, almost as a bit of a joke amongst a couple of friends having a drink one Sunday afternoon. They were joking about fashion trends and how the moustache had gone out of style. They thought it would be fun to bring it back. From that joke, they built a moustache-building themed month-long campaign with 30 friends.

They didn't raise any money the first year, but did start a conversation around men's health. The next year, they realized that their friend's mother was raising money for breast cancer research and they thought maybe they could raise a few thousand bucks for prostate cancer research with this idea. That's how it started.

In the twelve years since, we've raised $800-plus million. Millions of people have grown moustaches and millions of conversations around men's health issues have likely been had.

The money raised gets split into three main areas: prostate cancer, testicular cancer, and mental health/ suicide prevention.

We see ourselves as the leading global men's health charity. Everything we do has a gendered lens. Our focus is on men's health. Our vision is to change the face of men's health by ensuring that men lead happier, healthier, longer lives. Our raison d'etre is to stop men dying too young, whether by prostate cancer, mental health and suicide issues, or testicular cancer.

Within our prostate cancer portfolio we focus on three main areas: biomedical research, clinical quality registries, and clinically integrated survivorship services.

Clinical quality registries can be an enormously powerful way to rapidly improve the lives of many men by systematically understanding treatment practices in different markets and what drives improvements and excellence in outcomes. Armed with this knowledge and learnings, Movember (in partnership with clinical stakeholders) seeks to influence positive changes in clinical practice. If we know from a clinical registry that a subset of patients in a particular population is doing poorly in terms of patient reported outcomes—sexual dysfunction or incontinence after surgery, for example —then we can develop or connect interventions that effectively address these issues. It's all about better outcomes as reported by patients, not just what doctors say is good for patients.

We work with a lot of clinicians, patients, and epidemiologists and use patient-reported outcome tools to ensure the data is actually coming from the patient's perspective.

The other side of the prostate cancer equation is survivorship. We've got an exciting flagship program called TrueNTH that has a global investment of $45-plus million aimed at significantly improving the lives of men diagnosed with prostate cancer, as well as their families. We are funding a substantial portfolio of programs aimed at addressing and reducing the key physical and mental side effects of treatment across all disease stages. Interventions include decision support, tailored exercise programs, and symptom tracking that enables men to compare their progress against men at a similar stage of treatment and provides tailored tips and resources. TrueNTH is a holistic, multidisciplinary survivorship program that aims to provide support from diagnosis all the way through the prostate cancer journey.

For testicular cancer, we focus on translational research and understanding the biology of relapse. Ninety-five percent of testicular cancers are usually curable, but we think losing 5% of those men is unacceptable. We want to understand why some men relapse so that we can optimize their treatment options in the future.

Finally, in the mental health space, we fund prevention and early intervention projects aimed at keeping men mentally healthy and taking action early when times get tough. The projects that we invest in all have the potential to scale within and across countries if they are successful.

Why does Movember focus on funding global initiatives rather then individual projects within individual countries?

Dr. Buzza: To be honest, in the very early days we were making this up. I put my strategy-consulting hat on and thought we'd be able to benchmark collaborative efforts around the world. In the beginning, there was very little happening to actually benchmark.

From 2004 to about 2010, Movember didn't have any in-house investments, instead we funded research through our Men's Health Partners. Funds raised in Canada went to Prostate Cancer Canada. Funds raised in the United States went to the Prostate Cancer Foundation. Funds raised in Australia went to the Prostate Cancer Foundation Australia or BeyondBlue, the national mental health initiative. All funds went to partners.

After talking to our partners, clinicians, patients, and the community, we realized there was very little consolidation within the global research effort. Everybody had a national lens. No one was taking an international approach.

In 2011, Movember was growing exponentially from a fundraising perspective. We were operating across 21 countries, had quite a large global footprint, and thought we had an opportunity to take a leadership role on collaboration.

We started investing some of our own funds. There are now 27 of us around the world in the in-house program team.

We didn't have any models for global cooperation. The Michael J. Fox Foundation was doing some interesting things in terms of global clinical research collaboration, but that model didn't quite work for us in the biomedical and translational research sphere. There was an interesting company called The Myelin Repair Foundation that was doing some interesting collaborations between industry and academia, but it was mainly United States-focused.

We established a Global Scientific Committee of key opinion leaders in the prostate cancer field. Professor Colleen Nelson, Queensland University of Technology, the Chair of our Global Science Committee, has been a real champion for this collaborative model and continues to be an advocate for collaboration today.

It was a very organic process. In the early days, our Global Scientific Committee reached out to key opinion leaders in the Netherlands, Ireland, the United Kingdom, the United States, Canada, and Australia. Everybody on the committee reached out to four or five respected clinicians and scientists in their own countries. We grew exponentially. Word spread that we were trying to work collaboratively.

We started talking to people in each country. We'd have teleconferences with up to 10 or 15 people in a country and it became clear very quickly that many people in different countries were working on almost identical research projects. From the very onset you could hear that people were stunned as they all went around the room saying, "We're working on that as well."

At that moment, we knew that we were on to something. We learned very quickly that there was so much duplication of effort and that hundreds of thousands of dollars were being spent on duplicate research projects with almost identical aims. We asked the question: why not get these teams of researchers to work collaboratively, dovetail their efforts, and integrate their research when it makes sense?

Once we got going, we realized there was an opportunity to expand our global teleconferences, so we split the conversations into different themes in the GAP1 biomarker project: urine biomarkers, blood-based biomarkers, and tissue biomarkers. We then separated everyone into global cross-functional, multidisciplinary teams.

We came up with a large team science model. We've got teams of researchers with very similar interests working on clinical questions that either matter to patients or will matter to patients downstream.

Operationally, we have a Movember Project Manager at the epicenter of each project setting the agenda and driving the project forward. Our Project Managers all have a strong background in science and project management. Many have a PhD in their field.

In those early days, that person was me. I was overseeing seven GAP1 projects. GAP1 is now essentially finished. Now my team members play the roles of Project and Program Managers.

What started off of as a $5 million investment in 2011 turned into a $9 million investment as we expanded out some important areas of the biomarker projects.

After the first year was successful—and we thought that we had the biomarker space well covered—we decided to expand the model out.

Now, each year or two we start to invest in a new GAP project. In 2012, we started the GAP2 imaging project by bringing the radiology, nuclear medicine, and medical oncology communities together. We brought on my colleague Sam Gledhill to lead that initiative, given his strong imaging background.

We funded four clinical trials under the banner of GAP2, each looking at new PET tracers to better detect metastasis and relapse after initial therapy. (The premise was that if clinicians could see metastases at a more granular level using cutting-edge PET technology, they could optimize treatment decisions that impact patients). That area of research has exploded in recent years as PSMA and other tracers have moved from research to prime-time. We are pleased that we were able to catalyze this field and are thrilled that we invested in PSMA in the United States and Canada very early on.

We've invested in some really interesting tracers, one of which was Fluciclovine (Axumin). A biotech company called Blue Earth Diagnostics picked up Fluciclovine (Axumin). We divested some of our funds and let them run with it. Instead, we initiated our testicular cancer program.

We see ourselves as a catalytic funder. Sometimes we fund research for the long-term, but other times we catalyze a particular area and then let it grow organically. Blue Earth Diagnostics have since gotten Fluciclovine (Axumin) FDA-approved, which is a really pleasing outcome or our early investment.

For our GAP3 project, we invested in a global Active Surveillance initiative because we wanted to ensure that men with truly low risk prostate cancer avoid a lot of the side effects associated with active treatment if at all possible. For our GAP4 project, we invested nearly $10 million into a large international clinical trial looking at the survival and quality of life benefits of exercise in men with advanced prostate cancer. Dr. Rob Newton co-chairs our GAP4 steering committee with Professor Fred Saad in Montreal. (See Prostatepedia April 2017 for a conversation with Dr. Rob Newton.)

GAP5 is our first testicular cancer initiative.

In essence, everything we do is about getting better outcomes for patients faster.

GAP1 is complete. Does that mean you won't fund more biomarker research?

Dr. Buzza: This question comes up a lot and it's a good one. The key consideration is: do we continue as a seed funder or do we pump more money back into a particular area of research that we feel is particularly promising? We assess this on a project-by-project basis and make a decision with our expert advisory committees as to what will likely have the greatest return on our investment for the men that we serve.

We focus heavily on the concept of knowledge translation and think about how we, as an organization, facilitate the knowledge generated from our projects to move through the development pathway so that the outcomes can hopefully change patients' lives quicker.

One thing we are exploring at the moment is the concept of a GAP knowledge translation symposium where we get GAP-funded researchers, industry representatives, policy makers, patients, and insurers or payers into the same room. Researchers will present their findings and say: this is the data from our projects. How can we push this forward in a collaborative way that leverages partnerships?

Behind everything we do is the concept of collective impact. (Read Dr. Buzza's article on collective impact at https://ssir.org/articles/entry/accelerating_mens_health_via_global_collaboration.)

The concept of the collective impact model is that it brings disparate stakeholders together within a system to address critical challenges and to drive positive change.

One of the five principles of the model is that a backbone organization

connects the various key stakeholders and acts as glue that holds them together. This organization drives the agenda, sets the meetings, and is responsible for pushing the actions forward. It is a hub-and-spoke model with the backbone organization in the middle of a range of other organizations all working together. Someone has to take responsibility for bringing everybody together and driving the change. It doesn't happen by itself.

That's what Movember is trying to do.

My role has morphed over the last 12 months. We now try to take more of a holistic approach to the $265 million that Movember has invested in biomedical research. I work very closely with our GAP-funded clinicians and researchers, as well as with the Research Directors of our Men's Health Partners across Australia, the United States, Canada, the United Kingdom, and Europe.

We're broadening the collective impact model we use in our GAP projects to include broader collaboration with our partners so that we can maximize the synergies within that funded research. What might that look like moving forward? Perhaps we'll move into theme-directed research, where a pocket of our community works on immunotherapy while another works on drug development, for example.

We will see what happens over the coming months in that regard. In the same way that we wanted to reduce duplication of effort and investment with GAP, we want to make sure we're efficient with all Movember-funded research.

That's the plan moving forward. Again, it's all about improving men's quality of life and reducing mortality.

It seems like a lot of your research projects focus on Australia, the United States, Canada, and Western Europe. Why are you not including researchers from Asia or Latin America?

Dr. Buzza: The easy answer to that is that the funds raised by Movember in each community are usually spent within that market and sometimes we have regulatory and legal obligations to ensure this. You can imagine that if you were a Mo Bro, or a donor in Switzerland, you may want that funding to go to Swiss research.

It's not always that clear-cut, but where we raise the funds is a key consideration.

You don't raise funds in Asia?

Dr. Buzza: We do. We raise funds in Singapore and Hong Kong. Singapore is involved in our GAP3 Active Surveillance project. In Hong Kong, we investment via a men's health partner.

We make investments through our partners in Singapore and Hong Kong.

Those are both English-speaking populations…

Dr. Buzza: Yes, they're English speaking.

We haven't had a formal Movember campaign in Japan, China, or India yet.

We also haven't had any formal involvement in Latin America through the Global Action Plan, but we're now starting to look at involving Brazil in one of our international clinical quality registries so that the data from men from Latin America are captured.

We do invest in a men's health partner in South Africa, but they're not involved in the Global Action Plan.

Are patients involved in any of the decision-making?

Dr. Buzza: Yes. We've got a patient representative on our Global Scientific Advisory Committee. Wes Sholes, a patient advocate from Los Angeles, lives and breathes prostate cancer advocacy. He does a lot of work with the Department of Defense and advises us from patient perspective. He brings a reality check to everything we do. He listens to the discussion and weighs in whenever he wants to. He is fantastic and brings us a real world perspective that only a man with direct experience can.

How do you inform patients about the results of your funded projects?

Dr. Buzza: We do a bit of that through our Movember marketing channels: communicating where the research funding has gone and what the project outcomes are.

But we're now thinking through how we can do that better. We want to better articulate the research highlights.

Through the knowledge translation symposium idea we're developing, there is an opportunity to do this. We'd like to help men with prostate cancer understand what the results are and why they will potentially be important to them down the track. One of the challenges is that this is detailed nitty-gritty science and it's quite a skill to articulate it in a way that is easily digestible.

So not necessarily understood by a lay population?

Dr. Buzza: Yes. We have a great in-house team that helps to translate the complicated scientific output into information more palatable to the layperson. Some of this stuff that we're funding is incredibly important, but it's incredibly hard to talk about say immunotherapy in a way that is understandable to a layperson. It's a challenge. That's the truth.

Can you speak a bit more about what happens to the data you produce? Is the data open to other researchers?

Dr. Buzza: We do have an online collaboration platform that we use to facilitate collaboration across countries and between teams, but that's not really public-facing. It's an online Wiki.

Each year, Movember-funded GAP researchers will produce a progress report, or if the project has finished, a close-out report. This is a ten-page executive summary outlining the research outputs, high-level data, and the publications arising from it. We always publish those close-out reports on the online platform so other researchers can read it, get a sense for the key lessons learned, and avoid the challenges that others have had.

We know that young researchers have looked at those reports and then taken a slightly different direction with their own research. It's knowledge exchange in action, especially considering that it could be a year or more from the time a researcher submits a medical journal article until it is published. We want to get better about making that data, that information, and those lessons learned available online to researchers in real time.

In terms of big data sharing, I don't think we quite have the skillset in-house to be doing that yet, but it's certainly something that is on our radar and something that we are keen to explore moving forward. Pp1

Clinical Trial: Jeff Lee Mobile Apps For Clinical Trials

Mr. Jeff Lee, a mobile technology veteran, develops clinical trial apps for most major pharmaceutical companies.

Prostatepedia spoke with him about how mobile technology streamlines the clinical trial experience for both patients and researchers alike.

How did you come to develop healthcare apps?

Mr. Jeff Lee: I have been in the mobile field for 20 years. For the first ten years or so, I provided mobile technology solutions to non-health industries.

I did a lot of random things: like helping Fox and AT&T do text message voting for *American Idol* contestants and other things for HBO, Disney, Discovery, National Geographic, among others. I helped the Obama campaign use mobile technology to engage people.

We used mobile technology to drive people to vote; drive them to stores; drive them to tune in.

In 2010, that company sold and I wanted to start something of my own. I was in the healthcare system quite a bit at that point. Within a 30-day period, both my parents passed away from cancer and my son was born.

My dad had prostate cancer that metastasized. First, he had had a fall and an ischemia event. He had all kinds of problems, but prostate cancer was the kicker.

I was very interested in health. I started thinking about the main areas of mobile technology. What I saw in my first decade in the industry was how powerful mobile technology could be at motivating people to take action: to adopt certain behaviors and to create connections between an organization and an individual.

A good friend of mine is a longstanding pharmaceutical guy with a PhD in Pharmacology. We got talking about how we could use mobile technologies in the health arena.

Like a lot of other people, I started off thinking about the obvious actors: payers, providers, patients, and employers.

Back then, mobile health was a burgeoning field and seemed a bit crowded, so we started thinking about clinical research and pharmaceutical companies. We thought this was an untapped opportunity and that we could do well by doing good.

A patient in a clinical research trial is generally there because they're unserved or underserved by existing therapies. They've been moved to enter a clinical trial, which generally raises stress and anxiety.

Now, the patient is in a study with clinicians who aren't familiar, who are serving as researchers. The patient takes a medication or has a treatment that is considered exploratory or experimental. There are a lot of activities a patient has to do in order to provide data back to the study and at the end of all that, they can be in very fragile emotional and physical states.

But a patient's activity in a study doesn't just impact him—it impacts science. It impacts everybody with that condition. If you blow off your therapy in your own personal treatment, you only hurt yourself. But if you don't adhere to a study protocol, you're hurting everybody who could benefit from the science learned in that study.

We thought mobile technology could help improve the clinical trial experience.

How are mobile apps used in clinical trials?

Mr. Lee: We've developed a mobile platform called Trial Guide that works on any study.

In an app store, you see ESPN, CNN, Facebook, Snapchat, and Instagram apps. Those are apps that do one thing. Inside of each of those apps are configurations that are specific to you. What shows up on your Facebook wall? The Facebook app morphs once you log in. ESPN morphs to show you your favorite teams and the score alerts you want to receive.

We've taken that same theme and applied it to clinical trials. We've developed an app to support classic areas of need in clinical trials that are very easily adapted to any kind of study.

One section of the app deals with things patients needs to know about their schedule of activities for a study. Not just when their next visit is, but what will be happening during the visit? How long am I going to be there? Do I need to fast? Do I bring my meds? Should I bring a book? Are there blood draws? Are there other things I need to prepare for?

There is also a diary section so that we can collect information about their response to medications.

A section deals with reference information. Any information you would normally get on paper can be put into the app.

A contact section makes it easy for patients to contact study researchers. All of these sections give patients support and guidance to proceed through the study. Every app is unique to every patient in a study. Patients enter an activation code and then the app initializes and sets up for their trial, their research site, their case, and where they are in the study.

This one-size-fits-all app has been used on hundreds of protocols, including prostate cancer studies.

Oncology patients are more intrinsically motivated than a healthy volunteer, but they have lengthy visits and have to better understand more information. (My eighth visit will be three times as long my sixth visit so how do I plan for it? I'm going to be really fatigued after my fourth visit, so I may need to take extra precautions. Having access to all that information is really particularly important in oncology studies, because those studies are generally more complicated.

Another challenge we see in oncology studies is that patients have a much greater sense of urgency about participating in a study. This may be a therapy of last resort.

Sometimes this means that patients are less likely to report negative symptoms or side effects because they're afraid that if they complain they may be dropped from the study. They gut it out and do everything they can to stay in the study.

Unfortunately, in many cases this means mild side effects that could be treated go un-discussed. The side effects become more severe and become a disqualifying side effect.

With oncology apps, we're trying to communicate to patients which symptoms should be reported. We want to help patients be proactive and confident in discussing topics, knowing that side effects can be managed and that they're better off saying something than grinning-and-bearing it.

Are patients are more likely to report side effects through an app?

Mr. Lee: There is a ton of evidence in the mobile health arena that tells us that patients are much more likely to communicate health issues, particularly stigmatized health issues, in a digital

fashion. For example, they're more likely to tell you their real weight than if they were talking over the phone.

But I don't know that we've got evidence that suggests they're more likely to report these issues through an app. Oncology clinical care is so high-touch and high stake. We're less focused on having patients communicate symptoms through a diary and more focused on encouraging them to have a conversation with their doctor.

Is the app only available in the context of a clinical trial?

Mr. Lee: Anybody can download the app, but it's not useful unless you have an activation code. The activation code is provided by the study.

Is there anything else you want to add that you think patients should know about clinical trial apps?

Mr. Lee: I had a lot of eye-opening moments when I came into this space six and a half years ago. One of them was the tremendous disconnect between clinical studies and patients. Only three percent of people who could benefit from clinical trials actually enroll.

I don't think many patients know how many sincerely passionate researchers are aching to find patients for their trials. There is so much energy and intense motivation going into creating these studies, making them run well, and helping create better patient experiences.

Sometimes a clinical trial can be a viable care option. If you're underinsured or have limited medical coverage access, a clinical trial can provide essential care.

Hopefully, more and more people will recognize clinical trials as a realistic alternative. Pp

Roni Zeiger, MD
Online Patient Communities

Dr. Roni Zeiger left a position as Google's Chief Health Strategist to explore the intersection of social media and health. As part of that journey, he created an online patient community called www.smartpatients.com.

Prostatepedia spoke with him recently about online patient communities and the power of connection.

How did you come to run an online patient community?

Dr. Zeiger: It's a hard question to answer. I'm on this very nonlinear journey that has included being a young scientist, then a doctor, and now a patient community builder.

When I was training to be a doctor and then practicing as a physician, I practiced in what I think is a very traditional way.

The reality is that we have an expert-centric healthcare system in which patients and families are generally thought of as passive recipients of hopefully high-quality care they're receiving from physicians and other members of the healthcare team.

That healthcare system doesn't work that well and most efforts to improve it continue to be expert-centric.

> *"Patients and families are generally thought of as passive recipients."*

It's about discovering new drugs and building better machines and designing smart hospitals.

During parts of my journey, while exploring how technology can improve healthcare, I accidentally started learning about the way patients were using the internet not only to find more information, but also to find each other.

That happened when I was working at Google, where I worked from 2006 to 2012. I studied how people use the Google search box to answer their health questions. While most people were using the search box to look for information, over those years an increasing number of people were looking for others with similar experiences.

If you think about it, connecting with each other in the context of our health issues is just normal human behavior. Yet, it's not something that we regularly think about when we practice medicine. I've informally polled thousands of physicians over the years and fewer than 1% of them have ever introduced one of their patients to another one of their patients. Isn't that amazing? That's not because we have discussed peer support and decided it's a bad idea. It's simply because it's not part of our training and not how we think. Our traditional medical model is designed for patients to receive good care from us and hopefully that works well.

I got obsessed with the idea of how can we take advantage of this underutilized resource in healthcare. How can we help patients and families find each other, support each other, and learn from each other in productive and respectful ways? How can we make that part of their healthcare experience —not something that happens behind the scenes?

What are the differences between online and in-person support communities?

Dr. Zeiger: I think the differences between online and in-person communities aren't as large as others might think. In both cases, it's about connection, support, and understanding that you're not alone. There are things that you can do in-person that are almost impossible online in terms of how you can

connect with someone—eye contact and even more obvious empathy. There are things you can do online that are hard to do in person: connect with more people who have had experiences just like yours, not all of whom can show up at the same time for a meeting because they're sick or they're far away or they had another commitment. Both types of support groups are complimentary and compatible with each other.

The biggest advantage of an online group is convenience. Assuming that you're comfortable being online, it's easier for some people to spend 15 minutes here and there interacting with their community, rather than meeting at a certain time far away from their homes each month.

Can you explain the concept of creating networks of micro-experts?

Dr. Zeiger: When someone in an online community poses a question, often a certain subgroup of that community gets most involved in the discussion. When a different kind of question is posed, a different subset of the community might have knowledge and experience related to that question or that issue. For communities that work really well, the idea is that the most relevant knowledge and experience surfaces in each conversation.

If you think about it, each of us is an expert in certain things that we've experienced or studied ourselves. Each of us is a micro-expert. Every conversation in a community is a unique combination of the perspectives of these micro-experts. This is very different from a model in which we decide that one person in the community is the smartest and everyone turns to him or her to answer questions. Instead, we have a community of

"I studied how people use the Google search box to answer their health questions."

many individuals who are dynamically learning from each other.

So then this is more of a collaborative team approach?

Dr. Zeiger: Collaborative and team. I love those words. That's right.

Are you saying that this online collective of patients can become members in a patient's healthcare team—just as the doctor, caregiver, and patient are team members?

Dr. Zeiger: Today this is still mostly happening separate from someone's experience with the healthcare system. But as a patient, you certainly can think of that online community as part of your team.

"Your readers could become a great resource for other patients."

Today, an online community wouldn't interact with the traditional parts of your healthcare team. You can imagine a future where that might happen. We just haven't figured out how to do that yet. A lot of community members do think of the community as a really important part of their team.

Can you walk us through how smartpatients.com works?

Dr. Zeiger: Smart Patients is really simple. It's an online space where patients and family members can learn from and support each other. Anyone can sign up directly for the prostate cancer community at www.smartpatients.com/prostatecancer.

After a quick sign-up process, you'll simply see a bunch of ongoing conversations. You can read the ones that seem interesting to you, participate in any conversations that you would like to participate in, and start a conversation if you would like to. That's it.

Many men with prostate cancer have other diseases—diabetes or other cancer types. Can a prostate cancer patient sign up for multiple communities?

Dr. Zeiger: We want to keep things really simple, especially because a lot of our community members didn't grow up with computers and social media.

Most people join a community, like the prostate cancer community, and then over time we make it easy for them to also see conversations about other topics that might be interesting to them like diabetes or dementia or heart disease.

They don't have to join multiple communities. We make it so that those other conversations just get incorporated into their simple community experience.

That seems very easy. I know other online communities ask you to join each individual group.

Dr. Zeiger: We've worked really hard to make it a simple single interface so that just about anybody can use it.

You also have a clinical trials section. Can you talk about how that works?

Dr. Zeiger: As we were building www.smartpatients.com, we got a lot of requests to make it easy for patients to search for clinical trials. There is a government-run database that anyone can access at www.clinicaltrials.gov, but a lot of patients find that difficult to use.

We created an easier way to access that same information and incorporated it into our community platform. It's really easy for someone to find a trial and start a conversation in the community about it. Patients will often find a trial of interest to them and then ask the community what they think about that trial or if they have other suggestions.

So you're pulling information about these trials directly from www.clincialtrials.gov?

Dr. Zeiger: Yes.

A patient, researcher, or pharmaceutical company doesn't need to post it to the conversation: the information automatically feeds into your platform?

Dr. Zeiger: Correct, we pull all of the trials from clinicaltrials.gov.

Is there anything else patients should know about www.smartpatients.com or the promise of online patient networks?

Dr. Zeiger: I think many of us underestimate how much patients know and how much they can support each other. Most of your readers could become a great resource for other patients by participating in an online community. It's not just about finding information you might need. It's rewarding to so easily be able to help each other. Pp1

Dispatches from the Hill: *Prostate Cancer + The US Government*

by Jamie Bearse

Mr. Jamie Bearse is the CEO of ZERO — The End of Prostate Cancer. ZERO is a United States-based nonprofit with a mission to end prostate cancer.

In the first of a quarterly series, Mr. Bearse updates us on American policies impacting prostate cancer patients.

Each year, prostate cancer advocates from across the United States storm Capitol Hill to fight for patients and families on important issues like: increasing prostate cancer research funding, expanding access to care, and generating awareness.

I've worked at ZERO for more than 5,500 days, attended 15 ZERO Prostate Cancer Summits, and met thousands of families fighting prostate cancer from all across the country. They come to D.C. ready for battle to make sure no one else goes through the pain and suffering they've endured.

We have had many successes through advocacy. The Department of Defense (DoD) plays a key role in fighting cancer. Through the Congressionally Directed Medical Research Programs, the DoD funds cutting-edge research. Specifically, ZERO's advocates spearheaded the creation of the $80M program years ago, stopped a $16M cut in 2011, and stopped it from being eliminated in 2013.

In my tenure, I haven't seen a federal budget proposal that did not threaten prostate cancer funding. Nevertheless, our advocates persist.

As a result, the Prostate Cancer Research Program has produced the discovery of three novel and impactful treatments for advanced prostate cancer—Zytiga (abiraterone), Xtandi (enzalutamide), and Xgeva (denosumab)—as well as a genetic diagnosis profile to determine aggressive disease.

But 2017 is a banner year! We have learned that funding for the Prostate Cancer Research Program (PCRP) at the DoD may be increased to $90M this year.

The Department of Defense's medical research programs are a proven business model and an epicenter for groundbreaking research in many medical fields, including prostate cancer. As part of this unique and successful model, the DoD program includes patients in a peer-review panel that chooses which bright ideas to fund.

With the additional $10M in funding, the PCRP will be able to fund as many as 40 new projects. Studies will investigate new tests for advanced disease, surveys to understand its genetic impact in families, and better markers to find the disease and put men on the best treatment pathway.

I started at ZERO in the communications department and I believe in the power of storytelling. This win is credited to the amazing advocates who never give up and speak with a unified voice to their elected officials every year. I'm tremendously proud of their passion and hard work. They are the champions for the three million prostate cancer patients in the fight now, the heralds of inspiring stories from families that have fought courageously, and the heroes for the generations to come.

Our work is not done. Not until we reach ZERO prostate cancer deaths. Our victory today must be defended. Call your Senators and Representatives to protect the $90M for prostate cancer research.

Funding for the peer-reviewed Prostate Cancer Research Program is appropriated under House Report 114-577 and Senate Report 114-263 in the Department of Defense Appropriations Act, 2017.

Many Vs Cancer
Crowdfunding Prostate Cancer Research

Dr. Jonathan Simons, Mr. Andy Astrachan, Ms. Colleen McKenna, and Mr. Tom Andrus are the driving forces behind Prostate Cancer Foundation's Many Vs Cancer (http://www.manyvscancer.org/) movement set to launch this month.

Prostatepedia spoke with them about the vision behind Many Vs Cancer and how it fits into the Prostate Cancer Foundation's research funding programs.

How did you become involved with Prostate Cancer Foundation and the Many Vs Cancer movement?

Mr. Andy Astrachan: In late 2013, my family doctor felt a nodule on my prostate during my annual checkup. My PSA was slightly above 1.0 at the time and up slightly from the year before. An MRI was highly suggestive of cancer. I immediately reached out to my friend Mike Milken for advice. Mike referred me to his urologist and introduced me to Dr. Jonathan Simons who runs Prostate Cancer Foundation (PCF). I feel very fortunate to have been able to plug directly into the PCF for guidance.

A biopsy confirmed that I had prostate cancer. A month later, I had surgery. A few months later, Mike asked me to join PCF's Board. I am honored to serve on the board for the benefit of all prostate cancer patients.

Ms. Colleen McKenna: As Andy said, he was diagnosed several years ago with prostate cancer and subsequently joined PCF's Board because of his relationship with Mike Milken.

When Andy joined the Board, the primary focus of PCF's communication was to the medical, research, and scientific communities. As a patient, Andy felt that PCF should also be focused on communicating with patients in a language that can be easily understood to provide them with the same level of information that he received from PCF. Andy understood instinctively that by tilting communication to the patient, PCF would not only help all patients in their times of need, it would also be able to connect and mobilize a massive community.

Step 1 was a brand-new website which was launched in October 2016.

Step 2 was an appeal to the community of patients and those who love and support them to crowdfund the money required to expedite a cure. The appeal became a global movement of millions of people called Many Vs Cancer. PCF has done amazing work funding the most critical research over the last 24 years. The results of that work put us on the precipice of a cure. Now is the time to finish the job.

Andy recruited me to work for Many Vs Cancer and I immediately thought of involving Tom Andrus, with whom I'd worked at a company called Symantec.

Mr. Tom Andrus: In 2010, my wife Anne was diagnosed with Stage 4 appendix cancer. It had spread throughout her abdomen. We did everything that well-informed, connected people do. We worked with all the major leading hospitals. We did everything that we could do.

One of the things that she said to me was, "I'm hopefully going to be one of the first people cured of this. If not, I'll be one of the last to die from this cancer." She made it about two years.

At the time, precision medicine just wasn't there. You could see, though, that if we knew enough about people's cancers and their tumors we could come up with ways to precisely treat and not just use blanket radiation or surgery or chemotherapy.

Colleen introduced me to Dr. Simons who explained that in the last five years the prostate cancer arena has changed radically: there are now 19 precise targets in prostate cancer and multiple trials in place trying to figure out what type of treatments you can do for each of those different

genetic markers. Dr. Simons also explained that because of genetic overlap, the work we do in prostate cancer research will improve treatments in many other cancers, including, colon, ovarian, and breast cancer.

When Colleen reached out to me, I was ready for something fulfilling to do. Something that would change the world. After listening to Dr. Simons and Andy Astrachan explain their vision for PCF digital to democratize the dissemination of information to all patients and for Many Vs Cancer to empower all patients to participate in curing cancer, I felt compelled to sign on.

I have a long history of building tech companies. I thought if I can put what I've learned into such an important cause, we could educate patients about the power of precision medicine, empower them to participate in fundraising, and engage them in the science, that would be the best thing I've ever done.

What is the Prostate Cancer Foundation's mission?

Mr. Astrachan: PCF is the world's leading philanthropic prostate cancer research organization and is certainly among the most effective cancer research organizations of any type in the world. For the past twenty-four years, PCF has raised over $700 million for research, funding over 2,000 groundbreaking research programs at over 200 cancer centers and universities in 19 countries. We've funded 3 Nobel Laureates and many hundreds of leading scientists in the fields of genetics, immunotherapy, and big data analytics from cloud computing.

Since inception, PCF has been a pioneer in new drug development, providing key funding for FDA-approved treatments that improve survivorship. Thanks in large part to the work of PCF researchers, in the last decade six drugs for men with advanced prostate cancer have been FDA-approved. Of those six drugs, five were FDA-approved because they actually prolonged patients' lives, rather than simply easing their symptoms.

The $700 million raised directly by the PCF has attracted an infusion of more than $10 billion additional funding for prostate cancer research from government agencies, venture capital investments, the pharmaceutical and biotechnology sectors, academic research centers, and other philanthropies. In the United States alone, these new treatments have saved the lives of hundreds of thousands of men.

PCF has reduced US prostate cancer deaths by 52% in the past 20 years according to American Cancer Society statistics.

Mr. Andrus: Mike Milken founded PCF when he found out that he had prostate cancer. At the time, there was very little, if any, prostate cancer research going on. He set up the foundation with some very forward-thinking thoughts and processes on how research should be funded.

We're fast. We're open. Our approach is to get people funded quickly. We promise to decide on an applicants' grant proposal in 60 days as opposed to the year or more it takes for a big NIH grant. We also require all our researchers to share their information with PCF in real time and with each other, even before they're published. We select and coordinate *Dream Teams* across different organizations and sometimes continents to conduct research.

PCF specializes in early-stage or venture funding of research ideas. A lot of the recently-approved prostate cancer treatments came from our early-stage funding after which drug companies, governments, and other institutions put up a lot of money. But it is PCF that gets the ball rolling by funding the initial science. Thereafter, every dollar we put into research ends up being matched 20 to 30 times by the government or a pharmaceutical company to get drugs to market.

Ms. McKenna: Mike Milken took the model he utilized in his investment career and applied it to scientific research. PCF employs a venture philanthropy model that identifies those researchers with the greatest promise. Included in this model is PCF's Young Investigator Program. Like a farm team in baseball, the PCF Young Investigators are the brightest young scientists around the world who are identified early in their careers and supported with smaller grants that give them a chance to develop their science. A number of Young Investigators have gone on to develop important research.

Talk to me a little bit more about the kinds of research you fund?

Dr. Simons: One of the best examples of our international collaborations is the PCF Dream Team led by Dr. Arul Chinnaiyan of the University of Michigan, Dr. Charles Sawyers of Memorial Sloan Kettering Cancer Center, and Dr. Johann de Bono at the Institute of Cancer Research/Royal Marsden in the United Kingdom. The Dream Team was awarded $10 million and has sequenced the genomes of over 500 castration resistant prostate cancer tumors and identified the prostate cancer genomic landscape.

Through this team and another Challenge Award team, we supported de Bono's TO-PARP trial that found patients with DNA damage repair mutations may benefit from treatment with the PARP-inhibitor Lynparza (olaparib). (See Prostatepedia June 2016 for a conversation with Dr. Joaquin Matteo about the TO-PARP trial). That Dream Team also found that 1 in 9 metastatic prostate cancer patients have cancers caused by inherited DDR mutations, which has implications for treatment. Family members should also be screened for the mutation.

Current treatments we have funded include Zytiga (abiraterone), Xtandi (enzalutamide), and Taxotere (docetaxel.)

We've also funded the development of a precision medicine platform for prostate cancer and the development of prostate cancer *organoids*, or laboratory-grown mini-tumors that serve as avatars for studying tumor biology and drug sensitivity.

Other promising treatment approaches we are funding include therapies that target mechanisms of resistance to androgen receptor-targeted therapy, such as inhibitors of glucocorticoid receptor (GR) therapies, which target constitutively active androgen receptor-variants and extreme androgen receptor-pathway inhibition.

We're also funding several immunotherapies that will enter clinical trials this year: CAR T cells that target Prostate-specific Membrane Antigen (PSMA) and Prostate Stem Cell Antigen (PSCA) and vaccines against Prostatic Acid Phosphatase (PAP)

We're funding several clinical trials that look at combining radiation therapy with immunotherapy, as radiation may sensitize tumors to immune-killing and promote the activation of immune response. (See Prostatepedia April 2017 for a discussion with Dr. Emmanuel Antonarakis about such a trial.)

Lastly, we've recently launched an initiative to bring precision medicine into the Veterans Administration (VA) system, so that every veteran has the best level of care available. The sacrifices American veterans have made for all of us have earned them not only our everlasting respect and gratitude, but also the best standard of care and the benefits of the latest medical breakthroughs. The United States Department of Veterans Affairs (VA) works to make sure they receive both —and more.

We plan to invest $50 million over the next five years in a precision oncology initiative to expand prostate cancer clinical research among Veterans to speed the development of new treatment options and cures for prostate cancer patients. Approximately 12,000 veterans are diagnosed annually with prostate cancer.

Given the demographics of our veterans, prostate cancer is an especially urgent issue. One in eight men will be diagnosed with prostate cancer. It's the most frequently diagnosed cancer among veterans, accounting for a third of all male cancer cases. African-American men are 64 percent more likely to develop prostate cancer than any other race or ethnicity, and they're 2.4 times more likely to die from the disease. Yet we know little about the biological reasons for these disparities.

The timing of this partnership is crucial: never in history have we been so close to solving so many medical research challenges.

Can patients donate to specific areas of research or simply to your organization as a whole?

Mr. Andrus: Right now, they fund the Foundation directly.

Ms. McKenna: We haven't made a concerted effort to market PCF to the general public. Our Board feels that PCF is the best-kept secret in medical research. But that is now about to change with the launch of the Man Vs Cancer movement. In the past, our focus has been on relatively larger donations that are not earmarked specifically with the exception of grants in support of a specific young investigator or a Dream Team. That too will change with Man Vs Cancer, which will allow more targeted donations by scientist, by gene, or by research center.

Mr. Andrus: One of our goals is to empower people to not only give money, but also to participate.

The Man Vs Cancer movement is your brainchild, Mr. Astrachan. Can you speak a bit about your vision?

Mr. Astrachan: As a PCF Board member, I quickly understood that the rapid pace of medical research demanded greater funding than our historical fundraising model allows. We have now identified all 19 gene targets and their biochemistry in driving prostate cancer. We finally have exact blueprints for precision cures and the miraculous science of how to target genes is thriving. And we have identified the researchers capable of doing this kind of research. This is the golden age of prostate cancer research and now is the time to fund aggressively and finish the job.

PCF now stands on the precipice of curing prostate cancer. Prostate cancer will be the first major cancer to be cured. At this point, it's all about money.

At one of the earliest Board meetings I attended, Dr. Simons made a compelling case for the idea that $1 billion in venture funding over the next 5 years would be sufficient to put next generation precision drugs into development for all 19 genes that can cause prostate cancer.

When I heard that I said to the Board, how hard can it be to raise $1 billion over the next 5 years? Because $1 billion over 5 years is 4 or 5 times what PCF historically raises, most if not all, of the Board looked at me like I was crazy.

But I am not crazy. I was just doing a different calculation than they were. I understood that by harnessing the power of technology, social media, social networking and crowdfunding, we could mobilize a massive global community of prostate cancer patients and their loved ones into an army with the collective financial power to fund our own cures.

As Dr. Simons talked, I made calculations on the cover of my board book. That math is compelling. There are roughly 3 million prostate cancer patients in the United States and many millions more worldwide in addition to many multiples of that number who love and support us. That is a huge pool of people. If only 183,000 patients—a tiny percentage of patients—give $100 a year for 5 years and recruit 10 people to support us with the same financial commitment, that amounts to $1 billion.

With that calculation, Man Vs Cancer was born. Man Vs Cancer aims to reach the millions of patients worldwide and the far greater number of people who love and support us. The Many Vs Cancer global movement is by far and away the most ambitious and most powerful patient-lead community ever assembled for any disease by anyone for any purpose anywhere. Crowdfunding the last dollars needed for research from a vast audience of patients and our friends and loved ones means that by many of us doing a little, prostate cancer will be cured for everyone without overburdening anyone. Some of us will give money, some of us will organize fundraising events and teams, and some of us will do both.

As a patient, I know as well as anyone that all patients are willing to invest in research for their own cure as long as they have justifiable confidence that they're funding the right research being done by leading researchers and administered by the acknowledged global leader in funding prostate cancer research.

I believe our community will respond generously when it understands how close science is to delivering effective medicines, that many PCF-funded breakthroughs are currently occurring in small trials around the world, and how pivotal PCF has been—and will continue to be—in virtually every prostate cancer treatment advancement since 1993.

When does Many Vs Cancer launch?

Ms. McKenna: Mid May. We've just asked the first 1,000 members of our community to raise their hands to form teams and stand with us on Day One of launch. I thought it was going to take two months to get the first 1,000 people, but we've signed on almost 1,000 in a couple of days.

We're allowing people to take part in their own cure, to have a voice in the battle.

People are sharing their own personal stories. These stories of courage, a fighting spirit, and a strong desire to make a difference are amazing. It reminds me every day that what we're doing is important and right. Pp1


XTANDI takes on advanced prostate cancer while you take on what matters to you.
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AGAINST ADVANCED PROSTATE CANCER
Talk to your doctor and visit XTANDI.com/info
Please see Important Safety Information for XTANDI on the next page.
ONCE-DAILY
Xtandi®
(enzalutamide)
40 mg capsules

ONCE-DAILY
Xtandi®
(enzalutamide)
40 mg capsules

Talk to your doctor and visit XTANDI.com/info

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

Important Safety Information

Who should not take XTANDI?

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

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

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

How should I take XTANDI?

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

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

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

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

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

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

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

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

astellas MEDIVATION

QUESTIONS ABOUT XTANDI?

Call 1-855-8XTANDI (1-855-898-2634)

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

What is XTANDI®?

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

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

Who should not take XTANDI?

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

What should I tell my healthcare provider before taking XTANDI?

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

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

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

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

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

How should I take XTANDI?

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

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

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

The most common side effects of XTANDI include:

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

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

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

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

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

How should I store XTANDI?

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

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

General information about XTANDI.

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

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

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

What are the ingredients in XTANDI?

Active ingredient: enzalutamide

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

Marketed by:

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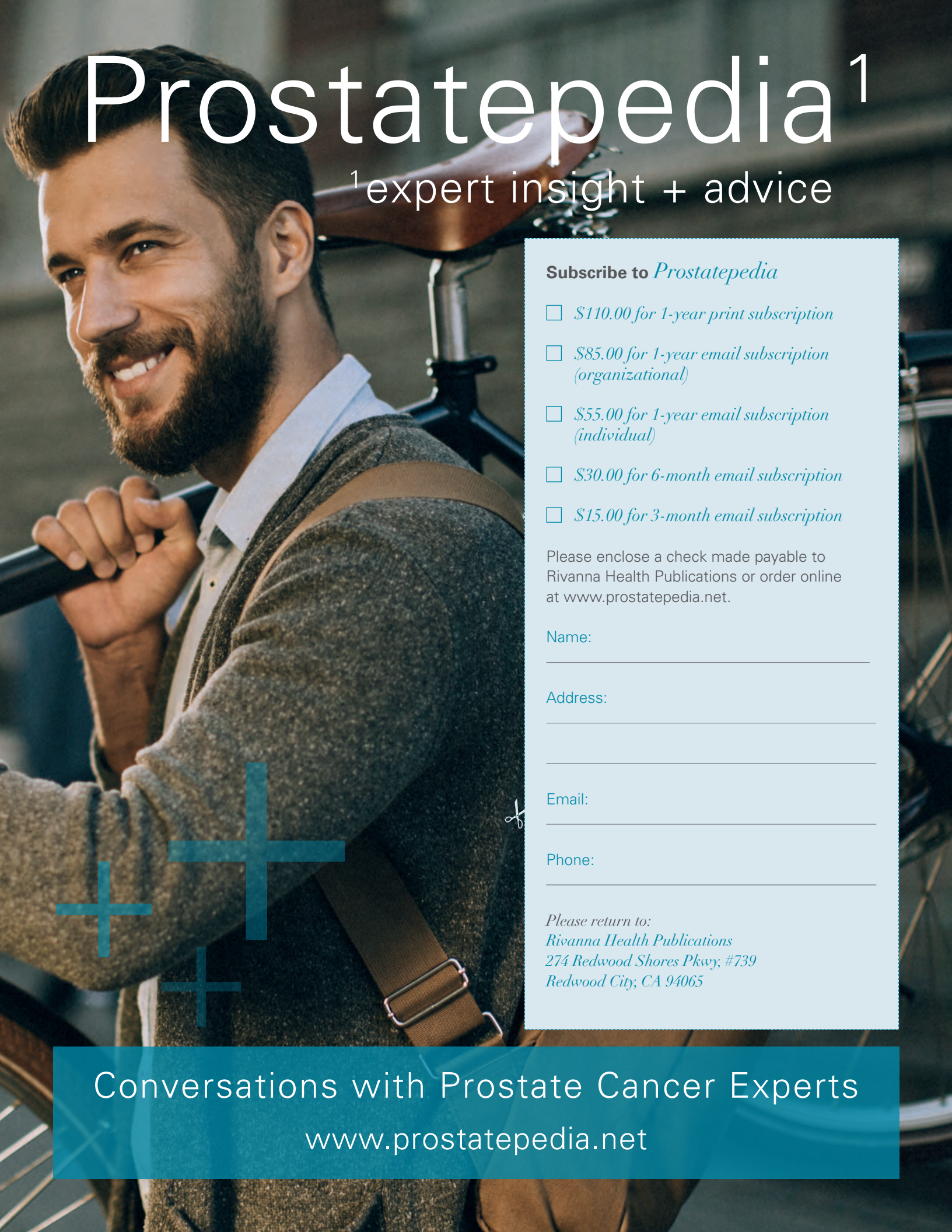
Medivation Inc., San Francisco, CA 94105
15I074-XTA-BRFS

076-1977-PM

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

Revised: October 2016



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WHAT IS ZYTIGA® (abiraterone acetate)?

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

IMPORTANT SAFETY INFORMATION

Who should not take ZYTIGA® (abiraterone acetate)?

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

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

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

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

If you are taking ZYTIGA®:

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

ZYTIGA® may cause serious side effects including:

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

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

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

- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems.** You may develop changes in liver function blood tests. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA® and during treatment with ZYTIGA®. Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - Yellowing of the skin or eyes
  - Darkening of the urine
  - Severe nausea or vomiting

The most common side effects of ZYTIGA® include:

- Weakness
- Joint swelling or pain
- Swelling in your legs or feet
- Hot flushes
- Diarrhea
- Vomiting
- Cough
- High blood pressure
- Shortness of breath
- Urinary tract infection
- Bruising
- Low red blood cells (anemia) and low blood potassium levels
- High blood sugar levels, high blood cholesterol and triglycerides
- Certain other abnormal blood tests

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

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

FOR MORE INFORMATION, ASK YOUR HEALTHCARE PROVIDER OR PHARMACIST.

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

ZYTIGA® can interact with other medicines.

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

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

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

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

051527-160418

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

 08/16 013481-160817

janssen

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

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

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

ZYTIGA is not for use in women.

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

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

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

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

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

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

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

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

What are the possible side effects of ZYTIGA?

ZYTIGA may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema)**. Tell your healthcare provider if you get any of the following symptoms:
  - dizziness
  - fast heartbeats
  - feel faint or lightheaded
  - headache
  - confusion
  - muscle weakness
  - pain in your legs
  - swelling in your legs or feet
- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems**. You may develop changes in liver function blood test. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA.

  Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - yellowing of the skin or eyes
  - darkening of the urine
  - severe nausea or vomiting

The most common side effects of ZYTIGA include:

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

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

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

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

How should I store ZYTIGA?

- Store ZYTIGA at room temperature between 68°F to 77°F (20°C to 25°C).

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

General information about ZYTIGA.

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

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

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

What are the ingredients of ZYTIGA?

Active ingredient: abiraterone acetate

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

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

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

051810-160421

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