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Welcome to Yale Cancer Answers with your host Doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it’s a conversation about prostate cancer with Doctor Michael Leapman. Doctor Leapman is assistant professor of urology at the Yale School of Medicine, where Doctor Chagpar is a professor of surgical oncology.

Michael, maybe we can start off by laying the groundwork and giving us a bit of a landscape of prostate cancer. How common is it? How lethal is it? Who gets it? Why should we care about this disease?

Prostate cancer is something that I think is always on our minds. We hear a lot about it on the news. It is the most commonly diagnosed skin cancer in men and over 230,000 American men are expected to be
diagnosed with prostate cancer next year. And it’s also the second leading cause of cancer death in men, and so that imbalance between how common it is and the risk of death from prostate cancer is really quite interesting, because the majority of men who are diagnosed with prostate cancer will not have a very aggressive cancer. But then again, there is a lot of aggressive prostate cancer that requires treatment, and so figuring out that balance, figuring out where one lives on that spectrum is really important. How does that happen? Is it a matter of seeing how aggressive the cancer cells look by their grade on a biopsy? Or are there other factors that kind of play into figuring out how aggressive this cancer is? A lot of factors really come together to help make that distinction about the risk level that someone has. Historically, we really had a very monolithic approach where if someone had cancer there was treatment right away. There was very little disconnection there. It was just kind of a one way path from a diagnosis of prostate cancer to treatment.
And that really continued for decades and decades until the understanding came that many of the prostate cancers did extremely well and probably did extremely well without treatment. And there was growing data and really strong information that these are very common in men in their 80s. They may be as prevalent as 60% of people might have a low grade, non aggressive prostate cancer. So this story began to be written over 30 years ago where there was increasing awareness of the spectrum of aggressiveness in prostate cancer and so the main criteria that we use to estimate a given man’s risk of prostate cancer and the risk of cancer will behave aggressively relate to what it does look like on under a biopsy, and there is a scale used called the Gleason scale, which is a pathologist will take a look at the biopsy under microscope and look at how normal or abnormal the cancer cells look. Look at the architectural pattern of the glands and assign a level. And that level is highly related to the outcome of the cancer.
So that’s a very good way of beginning to estimate the trajectory of prostate cancer. Some of the other tools we use, are PSA levels. PSA is a common blood test that is ordered and it’s a protein that is made by the prostate. And it can be found in the blood. Now, having a PSA level doesn’t mean that you have prostate cancer, but there is a relationship between how high that PSA level is and the risk that a man can have prostate cancer. So that level of PSA is also prognostic, meaning it can help us estimate how likely the cancer is to be aggressive or not. And the last classic thing that we do is a rectal examination of physical examination where we feel the prostate and see if we can feel a lump or a bump which is also kind of an indicator of how big a tumor might be, or if there’s something that has reached a significant level. So those are historically how we estimate aggressiveness and the appropriateness of treatment, or what treatment should be undertaken. So before we kind of dig into a little bit more on that...
just to take one step back when people often hear about PSA and digital rectal exams, they often think about screening more than they do about prognostication. And yet there have been some changes I understand to what people are recommending in terms of screening. So can you take us back and tell us a little bit about who should get screened when and with what? Should all men get screened if prostate cancer is really prevalent, or is there a benefit to screening? I’m so happy you asked that because I think begins to speak to the heart of the controversy and what I see in my daily practices. There is so much ongoing communication about that and different perceptions about screening. And so the story does go back even further, again, probably several decades ago when that PSA blood test was discovered in the late 1980s, and they found that if you check PSA you will find some people who have abnormal PSA levels, and we typically do a biopsy next and we’re
identifying prostate cancer so historically,
back in the late 80s and early 90s and into the early 2000s,
there was a lot of PSA testing.
It was routinely used in pretty much all men,
and a lot of prostate cancers were being found as a result.
And so you know,
it became clear that since a lot of prostate cancer is being detected,
more rigorous evidence was needed to be undertaken so very large national and International Studies were done to look at the benefits of PSA testing to determine and really quantify how beneficial it is to have a PSA checked and find a cancer that could be in the prostate which was previously undetected, because they generally don’t cause symptoms and so when we talk about screening, we mean taking people who have no symptoms who are otherwise, well.,
they have no evidence of prostate cancer,
but trying to find something early before it is manifest before it comes to the surface.
And a few studies have been done, and one landmark study was performed in the United States which really didn’t find a big survival benefit to screening. And so as a result in 2012, the US Preventive Service Task Force, which is a guideline issuing body in the United States, said that because of that absence of benefit and the great potential for harm by treating that no men should undergo PSA testing under any circumstance. It was kind of a blanket recommendation. And this was really kind of a controversial statement for people, especially in the prostate cancer field, because it was clear that in the 20 years where prostate cancer screening was occurring, there was a substantial reduction in the risk of death from prostate cancer. And so right after that guideline came to be, there was another study which finally came to fruition, which had been conducted for over 10 years, but the results weren’t available, which was performed in Europe, which did find a large benefit to screening with PSA in terms of reducing the risk of prostate cancer death. So here you have these two conflicting
randomized trials which create a lot of uncertainty at which and there's still a lot of controversy about which one is right and which one is flawed. There are some substantial flaws with the study performed in the United States because many of the patients who were in the trial were actually already screened for prostate cancer, so it was a bit hard to distinguish those who had been screened already versus those who were not being screened. So it was almost as if everyone was really getting the same thing. So the controlled element of the trial was hard to appreciate. So that's kind of a long winded way of saying that it's still a very controversial question, but the evidence has really continued to accumulate as these studies have been followed for more and more years, and it really does appear to be as a substantial risk reduction in death from prostate cancer by having a PSA checked and finding
0:09:20.18 –> 0:09:21.82 early stage cancers and
0:09:21.82 –> 0:09:24.388 so do you recommend that for all men
0:09:24.388 –> 0:09:28.559 or men over a certain age or men with a
0:09:28.559 –> 0:09:30.038 certain demographic characteristic?
0:09:30.04 –> 0:09:32.12 I mean, perhaps the difference
0:09:32.12 –> 0:09:34.2 between the two studies and
0:09:34.273 –> 0:09:36.208 I'm just surmising here,
0:09:36.21 –> 0:09:38.265 maybe that there were different
0:09:38.265 –> 0:09:40.32 characteristics of the people participating,
0:09:40.32 –> 0:09:43.001 such that some men may
0:09:43.001 –> 0:09:45.126 really benefit from early detection
0:09:45.126 –> 0:09:47.719 and other men, not so much.
0:09:47.72 –> 0:09:50.41 I think you're absolutely right.
0:09:50.41 –> 0:09:53.168 And so we really kind of
0:09:53.168 –> 0:09:56.712 have to be anchored in what the
0:09:56.712 –> 0:10:00.102 studies have shown and the studies
0:10:00.11 –> 0:10:03.107 in both Europe and the United States,
0:10:03.11 –> 0:10:06.098 really focus on men in their 50s and 60s,
0:10:06.1 –> 0:10:08.375 and so the best evidence would suggest
0:10:08.375 –> 0:10:10.979 that men who are above the age of
0:10:10.979 –> 0:10:12.966 75 really don’t benefit very much
0:10:12.966 –> 0:10:15.096 from having a routine PSA checked.
0:10:15.1 –> 0:10:17.692 Now it’s a different story if people are
0:10:17.692 –> 0:10:19.911 having urinary symptoms or have a reason
0:10:19.911 –> 0:10:22.419 to suspect that they have prostate cancer.
0:10:22.42 –> 0:10:24.418 But when we talk about screening,
0:10:24.42 –> 0:10:25.748 we’re saying being asymptomatic,
0:10:25.748 –> 0:10:26.744 having no problems,
0:10:26.75 –> 0:10:29.27 but getting a PSA checked and going
0:10:29.27 –> 0:10:31.43 looking for potential prostate cancer.
0:10:31.43 –> 0:10:34.321 So the US Preventive Services Task Force
which issues these guidelines in 2018 revised their recommendation to suggest that prostate cancer screening with PSA can be considered kind of in a shared decision-making fashion, which means that a patient and their physician should have a conversation about the potential harms and benefits, and find a way to balance the potential harms of undergoing a PSA test, which could include having a prostate biopsy, having invasive testing or finding a cancer which is non aggressive and might not have changed their life expectancy. And balancing that with the potential benefit of reducing their risk from prostate cancer death so it is really kind of not a one size fits all approach, but it really should occur for men who are in the age of 55 to 69, which is kind of the recommended group. Some demographics appear to be higher risk and we do recommend earlier screening beginning at 45 and potentially even earlier for people who are falling into a high risk demographic based on a strong family history of prostate cancer, and that means having a first degree family relative.
with prostate cancer,
such as a brother or father.
Or having a known genetic alteration,
such as a mutation in the BRCA2
gene which is known to be associated
with prostate cancer risk and other
certain racial demographics such as
African American men are at higher
risk for prostate cancer detection
and death from prostate cancer,
and so they also fall into a higher
risk category where screening may
be appropriate earlier.
But it’s definitely not a one size
fits all approach.
I do think that the way to do it
is to really have a thoughtful
conversation to understand
the whole picture here and
why we would even consider prostate
cancer screening what we could find,
what the outcomes could be,
what could happen
and so doing that in the context
of a relationship with a physician
or health care provider who
you trust is really important.
And going back to our
earlier conversation,
even if you’re screened and an
early prostate cancer is detected,
not all men will undergo treatment for their prostate cancer, right? So how do you decide who gets treatment? Who doesn’t get treatment, and what that looks like? 

Yes, and I think that has really been the transformational shift that has happened in the past ten years or so. And you know the harms of PSA testing really relate to treating cancers that we find, and there are real risks of cancer treatment, including changes to urinary function, and GI and rectal toxicity. So the big change is the acknowledgement that it is appropriate to not treat initially patients who have cancer that appear to be non aggressive and that is a process that we call active surveillance, which is a period of close monitoring of prostate cancer rather than immediate treatment. And so what’s so transformative about that is that it sort of allows us to have the benefits of early detection, which are finding potentially lethal cancers earlier, treating those ones and forgoing or deferring treatment altogether for...
those cancers that are non aggressive. So we’re going to have to take a short break for medical minute, but when we come back, we’re going to dig into who gets treated, how they get treated, and how we can really personalize treatment for prostate cancer. So please stay tuned with my guest Doctor Michael Leapman.

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This is a medical minute about breast cancer, the most common cancer in women. In Connecticut alone, approximately 3000 women will be diagnosed with breast cancer this year, but thanks to earlier detection, noninvasive treatments, and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer.

Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and...
eliminating some of the fear and anxiety many women experience. More information is available at yalecancercenter.org. You’re listening to Connecticut Public Radio. Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I’m joined tonight by my guest doctor Michael Leapman and we’re talking about prostate cancer and right before the break, Michael you were talking about the fact that some men can have what’s called active surveillance, just monitoring their prostate cancer, particularly if it’s found early. Because there is toxicity to prostate cancer treatment. But other men really do require treatment, so let’s dig into that group. How do you figure out who requires treatment and who doesn’t? Yes, so that is one of the really important things that we do at the time of diagnosis. So if a man has had a prostate biopsy, we detect prostate cancer, the first thing that we really want to do is is trying to gather all the information possible to come up with that estimate of what we’re dealing with.
And so, in addition to the things that we discussed previously, the Gleason score of the PSA level, the physical exam, there are other tools that can help us predict what we’re dealing with, what the outcome would be if we did treatment, or if we didn’t do treatment, and two of those tools that we want to talk about, one is called a prostate MRI, which essentially is a high resolution MRI of the prostate. That often actually precedes the biopsy and helps us to a more accurate biopsy by finding areas within the prostate that could harbor prostate cancer and allowing us to more accurately target them so that we can identify cancer. If we don’t find something, the absence of an aggressive cancer is also reassuring to us, so that is an important component that helps us identify potentially more aggressive prostate cancer that could be present. And again increasingly happens before the time of diagnosis. But we incorporate that information
0:17:26.5 –> 0:17:28.887 to help come up with a sort
0:17:28.887 –> 0:17:30.61 of an assessment of risk.
0:17:30.61 –> 0:17:32.556 The other are a host of validated
0:17:32.556 –> 0:17:34.121 genomic tests which measure expression
0:17:34.121 –> 0:17:36.473 levels of panels of genes that are
0:17:36.473 –> 0:17:38.39 associated with prostate cancer outcome,
0:17:38.39 –> 0:17:41.63 and so these are not the tests that tell you
0:17:41.63 –> 0:17:43.884 do you have a good gene or a bad gene.
0:17:43.89 –> 0:17:46.754 These are genes that we all have
0:17:46.754 –> 0:17:49.296 present in all cells and what what we
0:17:49.296 –> 0:17:52.071 do is we sort of look at the tumor
0:17:52.071 –> 0:17:54.564 tissue and we send it off to various
0:17:54.564 –> 0:17:56.154 companies that can perform these
0:17:56.154 –> 0:17:58.47 tests and essentially get a score back,
0:17:58.47 –> 0:18:00.756 which is an estimate of risk.
0:18:00.76 –> 0:18:03.889 An estimate of the likelihood of a
0:18:03.889 –> 0:18:06.357 prostate cancer spreading beyond the
0:18:06.357 –> 0:18:08.967 prostate or returning after treatment.
0:18:08.97 –> 0:18:10.758 Now these tests are not recommended
0:18:10.758 –> 0:18:12.93 for all men with prostate cancer.
0:18:12.93 –> 0:18:14.826 They are not an absolute requirement
0:18:14.826 –> 0:18:17.232 because if the cancer appears to be
0:18:17.232 –> 0:18:18.672 sufficiently aggressive based on
0:18:18.672 –> 0:18:20.518 their Gleason score or PSA level,
0:18:20.52 –> 0:18:22.5 there appears to be little utility
0:18:22.5 –> 0:18:23.82 in doing the testing.
0:18:23.82 –> 0:18:24.15 However,
0:18:24.15 –> 0:18:26.79 for people who might be on the fence,
0:18:26.79 –> 0:18:28.545 who maybe are considering active
0:18:28.545 –> 0:18:30.693 surveillance or treatment and want
0:18:30.693 –> 0:18:32.703 a bit more information about their
estimated prognosis or how they might do in either of those categories, these tests appear to have some value. And so putting all those together with of course very important things like a patient’s personal preferences, what they want, what their functional status is, what their age and their overall medical health is helps to create a more holistic picture of a man’s prostate cancer profile. And what treatment options or what management options would be appropriate. And tell us with that score, does it give men a concept of their survival rate or you were saying that it might give you a clue as to the likelihood that it’ll spread beyond the prostate, what are the tangible measures that men get with that information rather than simply a score, which can be kind of nebulous. The information that they provide there are a few different tests, and they kind of frame the information differently. But the two main measures that they provide are the risk of death from prostate cancer within 10 years.
And the other one would be a risk of recurrence of prostate cancer or metastasis from prostate cancer within five years, and so those are the estimates and keep in mind that these are not firm predictions because treatments have changed very much and they continue to change.

But these are still estimates and they really do appear to be valid at distinguishing more aggressive and less aggressive prostate cancer, and so knowing where those risk estimates live are important because I think they can help people make more informed decisions about #1 the necessity of treatment and #2 the intensity of treatment. So should I be treated altogether? Should my treatment include one form of treatment such as surgery alone or should I have surgery and radiation therapy or additional sequences of treatment?

Based on the risk level and so that premise of can I use genomic testing to make that decision is still being fleshed out a little bit.
kind of a toggle where it will say your risk of survival or distant recurrence or even local recurrence at 10 years is X, but if you choose surgery alone it will reduce it by this much. If you choose surgery and radiation it will reduce it by that much. If you choose systemic therapy, it'll reduce it by this much. Is there that kind of granularity in the data with a toggle switch that will help men’s decision-making that’s such a wonderful question that I think we’re not there yet because of the novelty of these tools, the novelty of doing active surveillance, we don’t have that longitudinal data yet. I think that is really the Holy Grail where if we could say, if you do active surveillance, your risk is X, but if you do treatment it would turn down to Y. But say if you had surgery as opposed to radiation, your risk will be A, so that is clearly, where the field is moving. It is a bit challenging because treatment for prostate cancer is very much up to the patients.
There are many other factors that lead to these things and so really to do that in a rigorous way, we would need to do a randomized trial where we say we're going to flip a coin and half the group is going to have surgery and half is going to have radiation and we're going to look at how the genomic test or the MRI predicted the outcome, so I don't think that's ever going to happen, where we're going to be able to modify treatment decisions based on that. But we're getting closer with other studies that are looking at genomics to help guide treatment, and stratify risk and predict response to various treatments. So I think that is very much where we should be going, but we're not there yet.

So Michael, you have mentioned surgery and radiation a few times and not so much systemic therapy. But when we talk on this show as we do a lot about genomics, very often we're talking about as you said,
genes that are turned on or turned off within a particular tumor. Oftentimes these are targets for various systemic therapies. Has that been looked at in prostate cancer? The cancer is interesting because I think in comparison to some of the other cancers, such as lung, that really do have these actionable driver mutations that there are drugs specifically targeting a certain mutation that has not really been the case in prostate cancer for many reasons. Number one, the main systemic therapies for people who have advanced or metastatic prostate cancer work by suppressing testosterone. Those are very effective treatments regardless of genomic profile, that is kind of the mainstay of treatment, and they almost universally have a good response. But there is increasing recognition that there are molecular and biomarker hallmarks such as homologous recombination gene mutations, microsatellite instability or DNA mismatch repair deficiencies that can lead to targeted treatments for men who do have metastatic prostate cancer.
and so that, I think is one of the big changes that has occurred in recent years, is the recommendation that we do germline testing for patients with regional or metastatic prostate cancer to see if they have an actionable mutation that could be targeted. And so kind of getting back to one of the confusing parts of terminology that I think a lot of our listeners might get mixed up about, it goes back to something you just pointed out. The difference between germline mutations and somatic mutations, so earlier for example you mentioned that men who had a BRCA genetic mutation may be at a higher risk of developing prostate cancer, but that is fundamentally different than this genomic testing that you’re talking about. Can you flesh that out for our listeners?

Absolutely, when we speak about these germline mutations we’re talking about the DNA that were born with that essentially has been inherited to us, which is in our germ line is present in all
of ourselves and they may predispose to the risk of developing cancer and the BRCA2 mutation is a very well acknowledged mutation that confers cancer risk.

When we speak about the panel genomic testing, we’re looking at relative expression levels, how turned up or turned down genes are within tumors, and these are not necessarily genes which have been inherited, or mutations within genes, but it’s a measurement of how active they are, so this is not a good gene or a bad gene, we’re wondering, how this was conferred, because genetics and prostate cancer risk is such a common question that we get because prostate cancer is very common and there’s a thought that many patients have that they inherited a certain cancer predisposition from a family member and that may be the case.

And there are certain well recognized genetic mutations that can be inherited in the germline, but we’re looking at levels of cancer levels of gene expression associated with the cancer outcome.
Yeah, and so you had mentioned that in addition to this genomic profile, that men will often make decisions based on other factors based on personal preference, but for a lot of men I can imagine that you know they come in and you say you’ve got prostate cancer. You know you can have active surveillance. You can have surgery, plus radiation and the genomic testing how to interpret that number, your 10 year disease free survival risk is going to be 10%.

What does that mean? Can you help us to understand how you discuss that with the patient and how they might factor in that information and what other characteristics or factors they may consider when trying to figure out how they should be treated? I can just imagine that they say look doc, I don’t want cancer. I want to live as long and as well as I possibly can. These conversations are universally difficult. I think having a cancer diagnosis no matter what the grade, no matter what the stage, no matter what your doctor tells you, is inherently an anxiety provoking
and stressful experience. There has been a lot of change, I think in the awareness of men of the fact that prostate cancer is very common, that the outcomes without treatment may be excellent, and so that has changed. A lot of men are expecting that diagnosis and have had friends or family members who have gone through the same thing. But still there is the kind of reflexive belief that any cancer risk should be reduced that you hear that word you want it out of your body. You want it treated, no matter what the consequences is, and I think that’s very often the initial reaction is I don’t care what it does. I want this gone. I want to treat it, and so that’s where I think building a personal relationship is so important to give people time, space, support for dealing with that and understanding what the diagnosis is and really in the cool light of day integrating all of the information and really trying to zone in on what the risks are, what the benefits are.
And it’s really not a one size fits all approach. Active surveillance is not right for everybody, but nor is treatment right for everyone. And so I think that really doing that in the context of a truly shared decision between stakeholders on the patient side and on the physician side are so important. These tools are just tools and the hope is that they do provide more clarity, but I don’t believe they’re sort of magically the answer. These tools are just tools and the hope is that they do provide more clarity, but I don’t believe they’re sort of magically the answer. And actually we are leading a study right now to help understand the personal experience and it’s an interview based study where we were interviewing people going through the experience and we essentially want to open the door and hear from them and learn what is the experience of having a prostate cancer diagnosis and what is the experience of having genomic testing? Does it help? Does it hurt? Does it create uncertainty? Does it alleviate uncertainty? And I’m very excited to be involved in that study. Right now I actually just came off of a call where we’re going through
these interviews and we’ve been so fortunate to have men share this very personal part of their lives with us and give us really new and what I believe will be transformative information about what it’s like to go through this. Because when these tests are studied in laboratories and by companies, there’s such an excitement to bring new technologies which do provide very helpful scientific information, but we’re trying to anchor it back to the patient level and see how this is going to help a given person. How is it going to help their family? And so that’s really what we’re interested in in the next step. Doctor Michael Leapman is assistant professor of urology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at yalecancercenter.org. We hope you’ll join us next week to learn more about the fight against cancer. Here on Connecticut public radio.