MODERATOR: Disclosures, none. I have not taken any money from pharma really in any capacity at all, knowing money things I do are expert witnesses and defense at the University's path. I do one funny, ha ha, funny Davies disclosure. I still believe in PSA screening for healthy men between the ages of 50 and 70 with greater than 15 years life expectancy after shared decision making process has been done. I always make a quick joke here on the next slide because it's my favorite slide, allow me to talk about myself.

I'm very funny. My interest principally are in pharmaceutical policy, which either gets you excited or quickly makes you very, very tired. I get excited, and I'm sure everybody knows, [INAUDIBLE] and this group. And I was able to join them a few years ago. And I've written a lot about shortages of blood-bladder cancer in *The New England Journal* once. And I'm just going to just talk very briefly about this article that's coming out. Hopefully, nobody gets mad at me about showing data.

Everybody has to have a COVID trial now. So this is my COVID study looking at erectile dysfunction drugs. And you'll see the dotted line for when the pandemic started. And you'll see on the bottom are controls are just BPH drugs, Finasteride and Flomax. Those are straight. And once the pandemic started, the urologist got busy writing lots of PDE5 inhibition medicines. And there's a pandemic on Cialis as a result.

It was kind of the flavor of the studies that is going to be in, thinking in a general, internal medicine publication soon. So that's the kind of thing I like to do academically than a lot of different versions of that. Anyway, what are we going to talk about today? So where are we now with the prostate cancer screening? What have we done?

We're going to talk about prostate cancer screening trials specifically. We're going to talk about some smarter screening options. And then I'm going to talk about my specific recommendations. Good. Submit objectives for the CME people after this. You should be able to lead a well-informed conversation about prostate cancer, early detection, and screening. You should be able to cite the shortcomings of the American trial, the PLCO trial.

You should be able to optimize evaluation of men prior to a urological consultation. And I think you should review people to talk about MRI data and order MRIs on your patients if you'd like to. I learned early on in my talking career that people generally only remember seven things in any one talk and even that probably is a stretch.

So in the back of my mind I'm thinking about the seven things I want everybody to remember, and maybe if you remind me, I'll refocus that. Whenever I talked about prostate cancer to internal medicine people I always think about these two books. One is *Invasion of the Prostate Snatchers* and the other one is do no harm by Dr. Brawley, who happens to be a friend of mine. And this is an outcropping of all of the terrible treatment that urologists are more than happy to do in the 90s inappropriately. And I always put my picture there the Davies is coming to get your prostate.

And these books are spot on actually. And Dr. Brawley's book, particularly the chapter on over treatment of prostate cancer, is spot on. So that needs to be acknowledged straight from the beginning. And I'm going to go through some slides on [INAUDIBLE] treatment. But urologists really were terrible, and still to this day they are terrible, about treating insignificant cancer. They treat it inappropriately. They treat it with the wrong types of treatment. And it's really a mark on our own profession that we've done that.

Just as a reminder in other countries-- people love it when I to do this. In other countries, like in England, for instance, or Germany or Sweden or Israel, 95% of low-risk prostate cancer is not treated, 95%. In America, that number is 50%. And that's a mark on our own profession. We should not treat low-risk prostate cancer. OK, just in terms of numbers, kind of quick and dirty here. This is one of those classic overdiagnosis tables that I love to show people. You can see our prostate numbers we've diagnosed at about 191,000 patients a year, yet only 33,000 die a year.

And this was a marked disparity in ratio between cases and deaths. And that's a marker for overdiagnosis. If you just walk down to lung and lung that's 160,000 are diagnosed with 72,000 deaths. And that's likely a more appropriate ratio. Prostate cancer though is this a growing killer and has been growing over the past few years. And it had been primarily going down Instance about 13%. The mortality rate internationally is about 7%.

It's not just America. It's not just a North American problem. People often think, oh, they don't see prostate cancer in Asia. No, they don't test for prostate cancer in Asia at all. So it's not that they don't die from it. They die from it in scores. They just don't do screening. OK, onto the important part the internal medicine people like to talk about. And this is the famous D recommendation in 2012. I'm well aware of that change.

But this rocketed prostate cancer. And it really made a forceful entrance into our life. And it was our fault. And how this came about we're going to go into. Why did the United States Preventive Task Force move to this grade D. I'm going to walk us through that a little bit. And I always put an acknowledgment. And I think I've said it enough. I'll try not to say too many times to bore the audience. But this was mostly our fault.

Urologists way overtreated low-risk prostate cancer. My favorite slide about low-risk prostate cancer is the old analogy to animals. And really low-risk prostate cancer is just like tumor A, it's a snail. It will never kill patients. If you really have Gleason 6 prostate cancer-- if you have a Gleason 6 prostate cancer, and it's treated, your chance of dying is 0%. Can you think of any other cancer that is 0%? No, that's because you don't need to treat it. That's why it's 0%. And that's tumor A, not needed to be treated.

The challenge with screening, as I'm sure everybody here is adept at knowing, is finding the tumor Cs. We want to find tumors that we can actually help people, much intermediate and high-risk prostate cancer. Tumor B is like the Gleason 3 plus 4s in an older gentleman. They'll never get to regional spread or metastatic spread. And we should actually not touch Grade 2 prostate cancer in older gentlemen. Happy to answer those questions later on how to do that. But really our focus is, as an epidemiologist, as public health officials, as urologists, is really to find tumor C.

The other thing I like to remind people at this point is there's no level of screening that I can offer, we can offer, the population that is going to cure us of prostate cancer. That will never ever happen. What we can do is good screening and help those that have tumor Cs. We're unlikely to be able to help people tumor Ds. And that's why the oncologic focus of metastasis is so important. We're always going to have people with metastasis. OK, enough of that kind of talk.

OK, these are the three trials, slightly related, that I like doctors to know about. The ERSPC, or in urology terms the European trial. The Gutenberg trial, which is a side offshoot of the European trial. I'll tell you why I like that one, just to break it out. Although, commonly, internal medicine physicians will yell at me for breaking it out. But I'm going to do it anyway. And the PLCO is the American trial. You'll see I have this sort of snapshots here.

The European trial updated in 2014, actually 2016. The [INAUDIBLE] has showed a 20% to 30% relative reduction in prostate cancer in their screening arm. And a Gutenberg trial, which was actually a real trial, showed a 42% relative reduction of prostate cancer. The PLCO trial, the American trial, showed absolutely no difference at all between the screening and non-screening trial. Let's just look at those briefly to kind of jump into them.

This is the PLCO trial. The first time I was published in 2009, and I was a new attending. I wanted to very much hide under some kind of rock. 80,000 people randomized annual screening, or a control group, under the rubric of usual care. And you can see over the years really no change at all between deaths to prostate cancer over time. This is led by urologist Dr. Andriole.

There were significant issues with this trial. We're going to go into them. As I mentioned, 80,000 people randomly assigned annual PSA screening for every six years versus usual care. Just some notes here. 52% of the men in the usual care group had at least one PSA test. So the control group-- I'm going to highlight this many times. The non-screened, quote unquote non-screened group, or usual care group had PSA testing done at 52% of the time when it was initially published in 2009.

And there was a very low biopsy rate of those with high PSAs. For some reason that was never really explained. There was no difference between the types of tumors seen in the screening and the usual care group. At the time of the publication, my two mentors wrote this kind of fairly brutal assessment, the study was not a fair comparison between screening and no screening, it was more a comparison of annual screening versus ad hoc screening, which is accurate. I mean, that's not really any argument about that.

It wasn't screened versus non-screened. It was a screen versus whatever the physician was feeling about the screening. It's a little bit worse than this as time goes on. And I'm going to welcome questions. And there are a lot of questions about this analysis. But this also came out of *The New England Journal* in 2016. And it looked at the screening arm, at the control arm, and calculated precisely how many, by survey, were screened in the control arm. If you do the numbers, it's greater than 90% of the control patients had at least one PSA.

That is not a screening trial by any measure that I'm aware of. So PLCO was not a trial of screening versus no screening. And if you do analysis, which has been done many, many times, including the United States Preventative Task Force. If you add this trial in in a traditional meta analysis, you'll have to explain to me how that can be valid statistically. I think sane people-- I mean, I don't want to ascribe a mentality to this. But it simply isn't fair to add a trial that isn't a screening trial to meta analysis of screening trials. Nonetheless, it was done.

You should know about the European trial. That is ongoing still and has a lot of interesting data points. It's a lot of European countries jammed into one trial. And the screening arm is barely screening by the way. It's only one PSA every four years. That's been published many times. So the first iteration of the publication came out in 2009, which showed a 20% reduction in prostate cancer death in the screen arm. And the screening arm is only one PSA every four years.

The updated version really was relatively impressive. That came out just last year. The number needed to invite, or number needed to screen, fell to 570. The number needed to be detected was only 18, which came from-- treated rather and diagnosed. I'm sorry number need to diagnosed to save man's life was 18. A much happier, updated version of the European trial. The Gutenberg trial is probably the urologist's favorite trial to show people because this is a real screening trial, with annual screening once a year.

And you quickly see separation in prostate cancer deaths at about the mark seven in a screening group, the first to control group. OK, number needed to treat was 12 in this one, as opposed to 18 in the larger. Anyway, because of that European data that came out, the United States Preventive Task Force did back away from a D and came to the C recommendation. OK, so we were happy about that. I do want to talk a little bit about the impact of that 2012 decision because it's been quite well-documented using both SEER data and MarketScan data That there was a significant impact to that change.

And I just want to dwell on this slide a little bit. And, hopefully, I can figure out how to do this without messing it all up. This is a new application of the PowerPoint. Let me just make that right. I want to show, here, this part of the slide because this is looking at low-risk, high-risk, and intermediate-risk prostate cancer over time since the new recommendations. Now, if I was an epidemiologist, what I would want to see-- I would exactly I want to see this blue line because that's low-risk prostate cancer not being diagnosed anymore.

Great, I don't want to diagnose low-risk prostate cancer. It's a waste of time. And it causes stress on patients. But what I would not want to see is that top line because that's high-risk prostate cancer, rapidly decreasing in diagnosis over time. So this is precisely what I would not want to see on the top and end in the middle, while the bottom one I would love to see. So it was sort of a dull knife approach to a problem because-- no that's probably poor word usage. But it was an approach to a problem that changed everything and didn't change the right things.

OK, so not only have we seen rates of prostate cancer go down, the wrong types of prostate cancer go down. We're now seeing a rise in metastatic disease, which may surprise people because you will see this is-- 2008 was when the change in the United States Preventive Task Force went to not screening 75 year olds anymore, which I actually think is the correct move. Nonetheless, that happened in 2008 and 75 years olds no longer really were screened.

There was a massive decrease in screening. And you'll see the metastatic rate increase over time since that recommendation. It had only gotten worse since the 2012 recommendation. You'll recall the PSA screening has a lot of faults. But one fault it is not is that is a very powerful way of getting rid of metastatic disease in our population. This was a nice publication done in 2015 in *The New England Journal of* Medicine, which showed the widespread screening in the 90s and mid 90s led to a massive decrease in metastatic disease in this country.

And you guys and gals treat metastatic prostate cancer. And you know horrible it is. And look how great the screening rates were at getting rid of it. Obviously, with all the attendant problems, which we'll go into-- but it did a very good job of getting rid of metastatic prostate cancer for many, many years. Unfortunately, I only have one slide on black and white differences in prostate cancer. And I do think it's important to highlight this. And I happened to be on the American Urological Association's Diversity, Equity, and Inclusion Task Force.

So I've helped develop some of this data. Hopefully, I don't screw this up. And for a long time urologists made quite a big deal and actually there are some guidelines still that exist that said, Black men should be screened more frequently. And that it was an independent predictor of death. And really is likely not true. And that race is not biology. Race is cultural.

There's no real biologic differences between white and Black men when it comes to prostate cancer. And it really shouldn't change anything we do in any way, shape or form in terms of treatment or screening. And it's going to take a while to get that out of people's brains in urology. And that's why our task force has a big job ahead of it. This is just one slide showing a recent publication that I had a hand in that came out in *Cancer,* showing really no difference between Black and white men treated across the board when using a good multi multivariable analysis.

So let's just summarize where we are now with PSA screening. In the 90s and 2000s, prostate cancer screening was implemented poorly. Everybody basically got it. Older men or screened, younger men were under screened, and low-risk disease was overtreated, and high-risk disease was undertreated. I don't usually like to write sentences in talks. But I like this one. We did try mortality down by 50%. I showed you *The New England Journal* where we drove down metastatic rates.

But it was at a huge cost, an entirely avoidable treatment and its attendant side effects. Screen none's not the right solution. We need to screen smarter. And that's what I'm an advocate for. To kind of highlight where we are just with the guidelines, the AUA, the American Urological Association, has specific guidelines for between 55 and 70 and with shared decision making. And the NCCN, similar, 45 to 75. The ACS starts at 50. The United States Preventative Task Force and AAFP, 55 to 69, recommend against [INAUDIBLE]

OK, so what are the goals of the smarter screen screenings, kind of meat of the talk. And now you kind of relax, throw eggs at me later. Meat of the talk. What do we want to do? We want to limit screening to healthy men who have greater than 15 years life expectancy. That to me is obvious, based on the data we have for treatment, which I haven't shown. But you'll have to believe me. We don't want to treat at all indolent disease. We a few caveats, which probably another great time to talk about.

Indolent disease, meaning low-risk prostate cancer, at Gleason 6, PSA less than 10. And if we do, we do not treat it. We just follow along. And for high-risk disease and for high-volume, intermediate-risk disease, we want to treat aggressively. So how we going to do that? Well, first thing, as primary care physicians, you should do baseline PSA testing is extremely powerful. Everybody should know that. If you have a gentleman with a PSA of less than one, you can safely not check their PSA for greater than years, actually probably not check it ever again.

But you can check it if you're on the nervous side every five years. One to two-- I'll show you the data on this in a second. One to two, recheck every-- I would err on the side of 12 months, not six. And certainly appropriate to send to urology if there's anxiety or family history. Greater than 2, I would argue, that would be a relatively aggressive referral. I'll have to check my slide here. I probably would change that to 3 or 4. should be sent to urology after a workup, which I'll describe.

And then over 60, I think, definitely less than one can recheck in five years. PSA 1 to 3, again, I think you would recheck in a year. And rethink about referral greater than 3 sent to urologists, maybe with an MRI. We'll talk about that in a little bit. OK, value of establishing an early baseline. OK, if it's less than one at 60, the likelihood of getting prostate cancer, and I'll show the data, is less than 0.3%. So if you have somebody, and there's quite a lot of people's PSA is really low, really don't need to check it again.

And not to beat a dead horse here, that should be one of our remembering points. PSA is less than 1 wait for five years for sure. In 90% of prostate cancer deaths occurred in men with greater than 2. It's pretty remarkable data. And this is the data. We don't have to really stare at it too much. But really when you look at the data it's really the top quarter of men with PSAs is greater than 2, which have any effect, really died from it. So less than that you're in good stead.

OK, so early baseline's a good idea. What else can we do? Well, we're going to talk about MRI here for about five minutes in the pre-biopsy setting. It's a very important new development in urology in the past five years that deserves our attention for at least five minutes, or six minutes. That's an MRI on the left. And that's a biopsy on the right. Now, what we did is we joined the MRIs and the biopsies together. And we get our diagnosis. I want to talk about one trial.

And if you can remember this trial, it's nice to remember it. It's a beautiful trial, very hard to do. I'm not sure we'd ever get this done in America. I don't think we would be able to. Let me describe it to you instead of reading my slide. This is a trial looking at how good MRI is versus-- so really the sensitivity and specificity of an MRI up front without a biopsy of predicting bad prostate cancer. And the way they do that it was a little bit mean, but this is a clinical trial.

They took men ages 50-70. And this is done in London. They took the men who had the elevated PSAs. And they said, OK, listen, my friend. We're going to put you to sleep. And one doctor is going to do a regular prostate biopsy that you would get anywhere in the world, including here in Pittsburgh, TRUS biopsy, 12 cores, and see what we get. And the other doctor, while you're asleep, is going to take every 3 millimeters a biopsy of your prostate.

It's called the template mapped prostate biopsy. Why would they do such a brutal thing to someone? They're doing that because they're getting MRIs on patients. And they want to be able to predict whether or not a patient has clinical disease with an MRI. And the only way you're going to be able to predict that is if you do a template-- I know every man is scrambling in their seat. To do a template biopsy every three millimeters on their prostate.

So let's look at what they found, Striking results from London. And that is if you compare the MRI, an upfront MRI. The sensitivity of finding clinically advanced, clinically significant disease is 93%. It's better than a standard TRUS biopsy. And, equally important, it's negative predictive value, meaning if it's a negative MRI, what's the chance of finding clinically significant disease? 90%. That actually there's data after this suggesting it's more like 95%. What does that mean for internal medicine [INAUDIBLE]?

If you order a prostate MRI and it comes back negative, everybody can calm down. A negative prostate MRI has a higher negative predictive value than an actual negative biopsy. Let's just repeat that. A negative MRI has a higher predictive value than a negative biopsy. And a positive MRI is more sensitive than a negative biopsy. So what this did was-- That very important trial, and very hard to do obviously, brought about this trial, the PRECISION trial, which was just out of last year.

And this trial, is also relatively straightforward, I had my hand in it, took men who are aged 50 to 70, randomized 500. Some men went to just the normal pathway like you would do in a normal urology situation. [INAUDIBLE] PSA. Go get your biopsy at the urologist office, or standalone surgery center, so they make more money. The other patients get the MRI before their biopsy. And this MRI and biopsy is the one I alluded to. This fusion biopsy where the images of the MRI are fused on to the ultrasound as we do it.

I'll show some pictures of that later, hopefully. Now, interestingly, in this arm on the left, the MRI before biopsy. If your MRI was negative, you did not get biopsied. So you can see how this is going to warm the cockles of your internal medicine hearts because you've got patients who are being not harmed by biopsies. And they're going to just be followed. Who is-- nobody. Tina Walker's texting. Hi Tina. OK, let's look at that look at the results. I'm going to quiz Dr. Walker on them later.

Precision results. MRI before prostate biopsy found clinically significant cancer and avoided 28% of biopsies altogether. And that section found much less indolent disease. So let's bring that up so we can look at it together. Now, remember, this is not going to capture as well as I'd like it to be. Lo sciento. But, anyway, you can see the group, the MRI-targeted biopsy groups on our left, 250 patients on the right side, is the standard biopsy group. That's just normal patients.

And if we just walk down into the area where we care about. So that's these patients, 7, 5, 3, 1, versus these patients over here. There's a significantly higher rate when the MRI targeted group, meaning in the MRI targeted group we found more disease, but we found less insignificant disease. Precisely what you want. This study is precisely why I advocate for MRIs prior to biopsies.

I'm not going to go through this. So just so we know. I'm going to spend-- this talk is rapidly coming to end. So everybody can throw out some questions. Just five more minutes left or maybe seven. For those of the uninitiated, I want to talk about transrectal biopsies because it's-- again, the men are squirming. It's unpleasant. You put a rectal probe in the behind. We look at your prostate through an ultrasound probe, and we put the needle through the rectum into your prostate.

And you can imagine that move of introducing E. coli and whatever other organisms living in your rectum can cause harm. They can cause severe harm. Our own institutional data would suggest 1% are admitted to the hospital for septic events. But the overall infection rate is much higher because most don't make it to the hospital. [INAUDIBLE] we stop them. That's more like 7% institutionally.

If you look at larger databases, the complications with transrectal prostate biopsy are even higher, depending this regional variation given microbiomes. But basically you're looking at a relatively high risk of infection. So you should be aware that this does not need to happen. And none of this needs to happen. And we started a procedure now that I started about a year ago called a perineal prostate biopsy procedure.

Again, every man here is squirming because they can see what's going on here. You sit in this new suite that Dr. Nelson built me. Thank you doctor Nelson. Then you put your legs up in the theater there. And then we have our computers to find your lesion that we have on the MRI. And then we put the needle into the prostate. Now, we do not go through the rectum for transperineal biopsies at all. And it's a relatively painless procedure. And I have data supporting that coming out.

Just to kind of get a look at what this looks like. Sorry guys, but this is the probe in the rectum. Now, we're not putting the needle through the rectum. This is the perineum right here. The needle goes right through the perineum into the prostate, and it's guided by MRI fusion technology, which I haven't shown here. It sounds fancy, but we're just simple surgeons. Basically when we fuse the two images a big bulls eye would be right here, and we just put the needle right in there.

Simple, simple it takes about five minutes. Since we've been starting-- this is just a screen of our data that I showed at a quality meeting. It's not a great slide. We've done about 100 now. We've had no septic events. Our patient reported outcomes are better than transrectal. And if you're looking for this data later, I'll go publish it as it comes along. OK, here's the money slide. Davies current recommendations.

Healthy men greater than 50 should, with greater than 15 years life expectancy, should be given the choice to screen in the shared decision making process, pros and cons. Obviously, I've sidestepped some of the cons here because that wasn't the point of the talk given to me. You should get a baseline PSA at 50. I would advocate, although it's somewhat controversial, get an MRI before biopsying the patient.

In Europe, this is standard. In England it's-- Sweden-- I mean, pretty much across the board it's standard. The American Urological Association does have it a as guidelines because [INAUDIBLE] has recommended. But it's not in the preferred guideline track yet. And I suspect it will be. Transperineal biopsy is much, much preferred than transrectal. As a department. We are slowly trying to teach and work ourselves through this.

It is a big ask to have people learn a new technique as I'm sure you're aware. That's a whole subject of the scholarly debate on how to make people do things. And I don't think you should ever treat low-risk prostate cancer ever. So if you can remember those five things plus the PLCO trial, I think you're going to be a great, and to continue to be great, internal medicine physicians. OK, that was my talk that I put together to kind of give you my schema. And I look forward to answering any questions.