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>> Hello and welcome to this task force interview. This is Howard Bauchner, Editor-In-Chief of JAMA, and I'm here with Alex Krist, a member of the U.S. Preventative Services Task Force. Hi, Alex.

>> Hi, Howard.

>> And as we do with each task force interview, can you describe who you are, how long you've been on the task force, and what your current academic and clinical practice is like?

>> Yes. My name is Alex Krist. I'm a family physician at Virginia Commonwealth University. I do research at Virginia Commonwealth University and then I practice and teach at the Fairfax Family Practice Residency. I've been on the task force for four years and I'm starting as the Vice Chair for the task force.

>> Thanks, Alex. I'm very pleased. We're going to be discussing a very long awaited task force recommendation statement. The title of the task force recommendation statement is Screening for Prostate Cancer, U.S. Preventative Services Task Force recommendation statement. We will be touching on the evidence report that accompanies it. It's entitled Prostate Specific Antigen Based Screening for Prostate Cancer, evidence report and systematic review for the U.S. Preventative Services Task Force. Alex, why don't we start with the precise recommendations, the grade level, and then we'll go into more the depth of the reasons that task forces made these recommendation statements.

>> That sounds like a good place to start. So, we're given a C recommendation for men age 55 to 69 years to get periodic prostate specific antigen based screening. And saying that this is an individual decision and we're recommending that men in this age group, 55 to 69, who are considering screening for prostate cancer talk with their clinician, understand the benefit, understand the harms, and make a decision about what's right for them based on their values and their preferences. We're also recommending against routine screening for men 70 years of age and older.

>> Alex, there's two high risk groups that I want to point out early in the discussion which the task force considers but does not make specific recommendations about. You could just mention those two high risk groups.

>> The two high risk groups are African-American men and men with a family history of prostate cancer. And we've taken a lot of time in the recommendation statement to talk about these groups and to call out the state of the evidence for these groups. And you're correct. We're not making a different top line recommendation. So the C recommendation applies to these high risk groups as well as to the general population and that has to do just with the state of the evidence.

>> Before we get into some of the facts and details, this is probably one of the better task force recommendation statements to talk about false positive, over diagnosis, and over treatment. People often confuse those terms and it's highly relevant to the discussion of PSA testing as screening for possible

prostate cancer. So can you talk about false positives, over diagnosis, and then concern about over treatment.

>> Yeah, these topics are critically important for this recommendation. So in this case, the screening test that we're talking about is the PSA blood test, the prostate specific antigen, and a false positive is referring to the fact that many men who get a PSA test might have a high value. And it's not related to prostate cancer. In fact, about 3 out of 4 men with a high PSA value don't have prostate cancer. So that's what we're thinking about for the false positives. When men have this high PSA, we need to think about what to do next. Diagnostically what we'd think about is something like a biopsy but this is something that has potential complications in and of itself. And men and their clinician might worry about why their PSA is high. Over diagnosis is referring to the fact that prostate cancer is a relatively unique cancer in that for some men, prostate cancer won't progress and it will never affect them in their lifetime. And the only they'd know they'd have prostate cancer is by getting screened for prostate cancer. So when we find these cancers, these are, in essence, over diagnosed cancers. And because we sometimes can't tell which cancers are going to progress and which ones we won't, we do end up treating some of these cancers aren't going to affect men in their lifetime. And that's what we think of as over treatment. And that potentially exposes men to harms from treatment who really don't need to have any treatments done to them.

>> Screening always involves false positives, over diagnosis, and then concerns about over treatment. And I think for people who really want to understand the concept of screening case finding at the population level, reading these two task force reports will really give people a great deal of insight about what's meant by these terms and their implications when you consider the population based screening.

>> Yeah. I agree 100%. And the -- a very unique issue too with prostate cancer screening around false positives is the rate of false positives depends a lot on what you define as an abnormal threshold. So if you're defining lower levels of PSAs as abnormal, then you have a much higher false positive rate. It also varies some depending on the population. And as men age, they're more likely to have a false positive.

>> So let's talk about first the importance of the problem. Why have people been interested in prostate cancer for many decades and this recommendation? How many people does it affect? What's the morbidity and the mortality associated with prostate cancer?

>> Prostate cancer is one of the more common cancers in men. About 13% of men will be diagnosed with prostate cancer in their lifetime. That number also depends on whether they choose to be screened or not. So among men who elect screening, there's higher rates of diagnosing prostate cancer for those over diagnosis rates that we're talking about. The other thing that's very important is that about 2 and half percent of men will die from prostate cancer in their lifetime. So it does have a pretty significant high mortality in terms of cancer deaths. And going back to those higher risk group, African-American men and men with a family history of prostate cancer almost have a double the rate of dying of prostate cancer as the general population.

>> Yeah, so based upon task force statement for African-American men, it's 4.2%. So essentially twice the overall rate of 2.5% and 2.3% for white men.

>> Exactly. Yes.

>> Now, you start screening. You do a PSA level and regardless of what you or anyone would characterize as being high, there's other conditions that can give you an elevated PSA level. And what are those?

>> Well, one of the more common conditions is an enlarged prostate. So benign prostatic hypertrophy. Other things that can cause an elevated PSA or any type of inflammation or infection in the prostate. Those tend to be more temporary but the enlarged prostate, the BPH, is something that will persist and result in a man having a high PSA for years to decades.

>> So that's the beginning with detection. Now let's turn to the evidence base and let's first put aside, we'll return to it, the multiple studies that have estimated the consequences of treatment. Let's talk about the three major clinical trials that have tried to answer the key question one, the benefit of screening. That's the CAP trial, the ERSPC trial, and the PLCO trial. Can you walk us through those three trials? In general, their size, how often screening was done, and what the principle findings were, and you can take them in any order you like but it's the CAP, ERSPC, and the PLCO trial.

>> Yeah, so let me start with the PLCO trial. So that trial was done in the United States. And they enrolled over 76,000 men and they randomized them to get a PSA test or not. And in this trial, they got a PSA annually. So every year testing and they followed men for 14.8 years. One of the criticisms of this trial and each one of these trials, they're very large and they're all done with great intent. And they all have some limitations. The PLCO's limitation is that there was a relatively high contamination rate in the control group. In fact, about 46% of controlled men got a PSA test in the year prior to this study and on average, in the intervention group, men had five PSA tests and control patients had about three PSA tests. Overall, though, in that study, it didn't show any reduction in prostate cancer mortality or in all cause mortality but there was a higher incidence of prostate cancer among the screening group. So they found more prostate cancers. So that was the main finding of that trial. There have been some subsequent modeling studies that looked at if we didn't have the contamination rate what would happen and there's some suggestions that it might be similar to the findings from the ERSPC trial. So moving next to that trial, that trial was conducted in seven European countries and I'll probably mainly refer to this as the European trial. And they enrolled 162,000 men. And in the different countries, they had a variable protocol. So the men got a PSA somewhere between every 2 and every 4 years. There was a variation in what was considered an abnormal PSA value. It was somewhere between 2.5 and 4. And then there was some variation in how men were treated afterwards based on if they were diagnosed with prostate cancer. But in that trial, they did find that there was a reduction in overall prostate cancer mortality among the intervention group compared to the control group. And so the relative risk of dying from prostate cancer was .79 and that was statistical significant but there was no difference in the all cause mortality. And the criticism or the limitation with the European trial is just the variation in the protocols across the seven different countries. And then the most recent trial is the CAP trial. This was done in the United Kingdom and this is often characterized as a trial of low intensity intervention for screening. So what they did is they randomized 420,000 men to either get a one-time letter invitation to get a PSA test for screening or to not get the letter for PSA test for screening. And among the men who got these letters, about a third of them in the intervention arm opted to get screened. And they didn't actually measure how many men in the control group got screened but what we know from the background rate of screening in the United Kingdom is it was probably about 10 to 13% of men who got screened. And what this trial found was that there was no difference in prostate cancer mortality or all cause mortality after 10 years of follow up between that intervention group and the control group.

>> Alex, thanks for the summary of the underlying findings of those two trials. Now there's many trials that have looked at the consequences of different treatments for prostate cancer and we will get to them but I'd like to walk through and I know people listening can't see it unless they have the actual article out but there's a table that the task force has produced that's titled Estimated Effects After 13 Years of Inviting Men Age 55 to 69 Years in the United States to PSA Based Screening for Prostate Cancer. And it's largely based upon the European trial but could we just walk through that from top to bottom because in some regards that's an easier way to digest the findings from the European study but it also integrates some of the findings from PAP [phonetic] and PLCO trial. So can we just walk through the table from top to bottom?

>> Yeah. So what we're looking at with this table is what happens to a 1,000 men invited to screening. And so we're starting with a 1,000 men. And if this 1,000 men get screened for prostate cancer, about 240 will have at least one positive PSA test. And then at least from what we know with the European trial where most men who had a positive PSA actually ended up going on to get a biopsy, 220 men would go and get a prostate biopsy. And from what we know about the complication rate of biopsies which is about 1% of men are hospitalized after getting a biopsy from these trials, two of those 220 men would be hospitalized. And then that leads to -- from the biopsy pathway, a 100 of these men who get a biopsy are going to be diagnosed with prostate cancer. So you can see a little bit of where the false positive rate is. It's that difference between the 220 and 100 men. And from what we know about more recent trends of treatment in the United States of active surveillance versus prostatectomy versus radiation, about 65 men of the 100 diagnosed with prostate cancer would get a prostatectomy or radiation. And 30 would be followed initially with active surveillance. So these are men who have a lower grade prostate cancer and have elected to do this treatment option compared to the other more aggressive treatment options. And among those 30 men in active surveillance, about 15 will progress and actually need to get radiation or surgery. And then from the harms data that we'll be talking about. About 50 men will have sexual dysfunction among the treatment group and about 15 men will have urinary incontinence. And then on the benefit, we'll prevent 3 men from having metastatic prostate cancer and we'll prevent 1.28 men from dying from prostate cancer. However, 5 men who got screened will still die from prostate cancer. So it's not preventing all deaths from prostate cancer.

>> I think it's these numbers that are derived largely from the European studies but others are really driving this C recommendation, a way in which a physician has to talk with the patient, try to educate the patient about benefits and risks, and then allow the patient to make the decision.

>> Yes, that's exactly right and actually, you know, Howard, one of the points that I think is so critically important about this data is whether screening is right for a man really depends on how they value these potential benefits and these potential harms. So men who are more concerned about prostate cancer and they're willing to kind of accept these harms of false positives, over diagnosis, and over treatment, there is a net positive to screening. And they might want to choose to get it screened. However, men who weigh these differently and they're more concerned about harms from unnecessary medical treatment and they're less concerned about prostate cancer, they actually would have more of a net negative and probably would choose to not to be screened for prostate cancer.

>> That's how this and some of the other screening tests that the task force deals with are so complicated. Let's turn more specifically to the harms because I think the task force does a fabulous job in always talking about harms and I want to make sure we reflect that in the conversation. So can you just walk us through what we know about the harms from treatment?

>> So the two more common harms that we think of from radiation and prostatectomy are urinary incontinence and erectile dysfunction. So those are the most common harms. The other treatment option that's on the table, though, is active surveillance and that involves watching PSA values, potentially repeating digital rectal exams, and repeating biopsies as well. So active surveillance has a set of harms related to the biopsies like we were talking before and also sometimes we want to be thinking about anxiety. And that can go across both groups but certainly with active surveillance they might be worried about if their cancer is progressing and other things. So that's an additional harm to be thinking about.

>> Thanks, Alex. Let's concentrate for a moment on screening for prostate in African-American men. I noted in this task force recommendation both at the beginning and then in discussions with you, that the task force spent a specific amount of energy and time on what we know about screening for prostate cancer in African-American men. Actually have an entire section in the task force recommendation that focuses on this. So could you just walk us through the burden [inaudible] evidence, potential benefits and harms, and then advising African-American men?

>> Yeah. So at its core, as we were talking at the beginning, African-American men are more likely to get prostate cancer and they're more likely to die from prostate cancer. So when we have a strong interest in trying to reduce this disparity and health outcomes. The problem that we have is that we really don't have enough African-American men who have been studied in these trials to be able to make a different recommendation for African-American men compared to the general population. So the PLCO trial only included 4% African-American men. And the European trial didn't differentiate the racial characteristics and looking at the different countries probably has a very low inclusion of black men in the trials. And similar with the CAP trial. So the task force found itself in this position that we really couldn't say whether African-American men would get any greater benefit from screening. And we really don't know if they'll have greater harms from screening. If the false positives, over diagnosis, and over treatments look different in these populations. So we're really trying to call out and make a call for more evidence here. We need more studies to be able to understand this balance of the benefits and the harms so that clinicians can better counsel patients. For right now, what we're suggesting is that the C recommendation for men 55 to 69 applies to African-American men and men with a family history. And so once again, this would be a discussion for men who are considering prostate cancer screening, between the patient and the clinician thinking about the benefits and the risks. And in this case, even thinking about well what's the differential risks of the disease? You know, that African-American men are more likely to have it and more likely to die from the disease and how does that play into how they weight the benefits and the harms to make a decision that's right for them. And if you think about for African-American men the increased mortality, I mean there's a whole host of factors that probably contribute to this and there's data supporting it. So you know, there's some evidence that the disease is different. There's some evidence that African-American men might not get as timely treatment or get the same treatment. And there's lots of other factors that kind of contribute to this and all of these have to be addressed to really reduce this health disparity.

>> The task force also makes specific recommendations about advising men with a family history of prostate cancer in the same way that they focused on African-American men. Can you talk about those recommendations?

>> Yes. So we have much of the same problem for men with a family history as we do for making a recommendation for African-American men. So in the PLCO trial, only 7% of men had a family history in that trial. So very similarly to African-American men, men with a family history are at a higher risk for prostate cancer and a higher risk of dying from prostate cancer. But also similar to African-American

men, we don't have enough evidence to make an assessment on the balance of the benefits and the harms of screening anything different than the general population. One unique issue for clinicians and patients to think about, though, with the family history is that there is a degree of family history. So, you know, men who have a first degree relative, a father or a brother who had prostate cancer, that's a greater risk than a more distant relative. And also if their family member had an over detected cancer, that may or may not put a man at greater risk. So we have to think not only about their family history and who it was but what was the type of the disease that they had. So a man who had a first degree relative and had a significant cancer, died from prostate cancer, that's a much more significant concern.

>> Thanks so much. Can we talk briefly -- this is -- you're not an expert in the treatment of prostate cancer but one of the struggles for the task force is that new diagnostic tests, new technologies are always being developed. And the task force has to make recommendations based upon existing data generally published and subject to peer review but there's always new advances. What have been some of the new advances? And you talked about follow up and I think that's really changed in the recent years. And there's also new genetics and scoring systems. Can you just briefly touch on some of the new evolving technologies that physicians who refer patients or patients themselves may see in terms of prostate cancer?

>> Yeah. So earlier I mentioned one of the challenges is differentiating men with prostate cancer that will progress and affect them in their lives versus the over diagnosed prostate cancers. And there's a lot of work going on looking at a number of different ways of kind of distinguishing the ones that are significant and the ones that aren't. And that work includes looking not just at the threshold of what the PSA value is but it involves looking at the change in time of the PSA. Their folks were looking at the percent free of the PSA versus the total PSA. And these are factors that I know clinicians will frequently use when trying to help patients think about whether to move onto biopsy for high PSA values. And then when men are diagnosed with prostate cancer, you know certainly we rely a lot on the Gleason score and looking at that. And there's new evidence and folks looking at MRIs to help with staging to try and figure out which ones are more significant. And then as you mentioned, there are genetic tests as well. And those are all still more in the experimental range and so all of these different elements of trying to mitigate and reduce harm going from deciding which men need biopsies to the best treatments for men. A lot of this is still evolving and didn't necessarily make into the level of evidence that the task force was considering in this review.

>> It's in part why I so enjoy the intellectual efforts of medicine because things are always evolving and changing based upon new data but as you mentioned, you know there's work on trying to understand two, should be biopsied and then there's a great deal of work on after people are biopsied what's the meaning of the biopsy and I think all of that is focused on trying to focus on those individuals who first should be biopsied. And then those who are biopsied who should be treated. And it's really an effective way of trying to reduce potential harms of treatment.

>> Yes, there is a lot of promise with that. Also the caution I would put in to is men are thinking about screening because there's a lot of promise and there's a lot of new look in this area, there may be a tendency for men to underestimate the potential harms. So that is still something for us to think about. So even though there is promise in differentiating who should be screened and who should be treated to mitigate those harms, you know we still have good evidence that those harms are going to occur no matter what even with trying to do our best to mitigate them.

>> Yeah, there's always so much excitement about, you know, the first publication in the specific area but you really need to test of the time and additional data to see how it really plays out over a course of a number of years or in a general population. And so I think there's often so much excitement initially and then with time, that excitement dissipates a bit.

>> Exactly, yes.

>> So two more questions and we'll return to the specific recommendations. When the task force draft recommendation came out, there was quite a bit of public comment. More than usual for some of the task force recommendations. Can you say how the task force responded to the public comments?

>> Well, we really appreciate the public comments and we also actively solicited input from topic experts like urologists and oncologists and surgeons and others. So those are very important to us and we spent a lot of time reviewing all of those comments and also waiting on the CAP trial release before finalizing our recommendations. We had a number of comments in different areas that helped us to better refine what we meant in our recommendations and to change some of the wording. So one of the bigger changes that you'll see is actually in the top line recommendation. We tried to be much more clearer about how patients and clinicians might think about whether screening is right for an individual man. We tried to really frame this as in the language of our C recommendation saying that, you know, this decision to get periodic PSA based screening for prostate cancer should be an individual one as opposed to making it sound like we were recommending a shared decision making discussions for all patients in all scenarios. We also had comments about the D recommendation for men ages 70 and older. There was some concerns that there may be some men over that age who may still want to be screened. And we have acknowledged in our clinical considerations that, you know, some men may still consider that they might want screening and that's something for them to talk about with their clinician. But we also tried to really explain better why we came up with the D for men over 70. There was some of a misperception that it was solely based on men's life expectancy. And it is partly that because as men age, they're less likely to have a cancer detected and have a treatment that they'll receive a benefit for in their lifetime. And partly due to the fact that prostate cancer's very slow growing. However, it also was based on a lot of data that the risks of biopsies and the risks of treatments go up as men age. And so there's higher rates of harms and the likelihood of having false positive also goes up. So we tried to clarify our thinking behind that D part of the recommendation as well.

>> How does this recommendation compare to the 2012 recommendation which, I think, you are well aware raised enormous amount of concern among certain groups? Physicians in the United States as well as patient groups.

>> Well, in many ways, the recommendations have a lot of similarities and I know folks often focus on the letter of our recommendations. They look at the C recommendation that there's a small net benefit or the D to not routinely screen men. In our 2012 D recommendation, we did have a lot of language in our considerations around the fact that some men are still going to want to be screened and some clinicians are still going to want to consider screening. And we were encouraged in our decision making in those scenarios. So this recommendation now just like in 2012, both of these scenarios, we're acknowledging that there are a few number of men who can benefit but there are many more who will have harms from this screening process. And that's very similar from 2012. And so just like in 2012, right now this is a complex decision on whether it's right for an individual man to be screened.

>> And recommendation of other groups?

>> So two other groups have recommendations that are similar to our C recommendation here. The American College of Physicians and the American Urologic Association both recommend shared decision making for men 55 to 69 every other year for prostate cancer screening.

>> Did the task force specify when they talk about a C recommendation and screening how often that should occur? Is it every year between 59 and 69? Is it every other year?

>> It would not be every year. In our clinical considerations, we talk about considering this every 2 to 4 years. And that's, you know, based on the European trial, the interval was every 2 to 4 years. We don't have any direct comparisons on the right interval for screening. However, there is some indication that less frequent screening than every year will also be one strategy to reduce potential harms.

>> As you know, I often towards the end of these ask more clinically oriented personal question. So I'll start with my own experience, I saw my primary care doc over at Northwestern a few years ago. And we were chatting and I asked him if I was going to get my PSA screening. He goes no, you know, it's a D recommendation. So they're recommending against the service. So I said well, I'd really like to have the screening done. So he said to me, well, you know if the PSA level's high it's going to create a problem. So I said to him, well that may be true but if it's low, I'll feel a lot better and in addition, if it's high, I have access to some of the smartest people in the world who can help me with my decision making. [Laughter] So it's so interesting how these recommendations play out in real life both on a personal basis as well as when you're acting as a physician.

>> Yeah. And I actually think that your story is a good one particularly in the context of a number of points. I mean we're trying to bring out that this is an individual decision. So I think this is an individual thing for patients and then I think there'll be a different interaction two for each clinician and patient kind of pair and how they'll talk about things. And there'll be many men who will make choices similar to yours and I think that you bring up the point that there's multiple time periods that an individual can make decisions. So there's one about whether to be screened or not. One about whether they get biopsied. Potentially one on treatment. So there's a number of opportunities that way and on the other hand, a lot of men will hear all the story of the pluses and minuses and say well that doesn't sound like a very good test. I don't want to do that. So it is very interesting how those personal beliefs and values kind of influence the decision process.

>> How does it play out in your practice, Alex? Because you know, this can take a lot of time. I mean I always worry about increasing number of recommendations, you know, that come under the rubric shared decision making. You know clinicians are busy. Patients are busy. You know tool aids have had mixed results. How does this play out in your practice?

>> I think there's a lot of people, myself included, who have concerns that this can take up tremendous amounts of time. And there is a risk for that. And it is something to be thinking about. You know I like to think that men deserve to understand the benefits and harms at some point in their life and to have those discussions at some time period. You know in practice for some men, this is a pretty easy and straightforward discussion. They might already know some about pluses and minuses. They might already be going in with certain beliefs and ideas. And they can be a quick kind of member fact checking experience to go over what a person is thinking and why they're thinking it. And come up with a very good decision. I think there are going to be some men that are going to want to spend a lot more time thinking about this and you know, for those men it probably is worthwhile for clinicians and patients to

set aside time and to do that. But over a man's lifetime, what I've often found is that there's a different series of conversations. There might be one where you're first introducing these ideas and there's a different one as you're following up over time and you're seeing them 2, 5, 10 years later after they've already been thinking about this. And those might be much more straightforward conversations.

>> Yeah, what you describe is the richness and importance of individuals having primary care docs who they trust and can see over many, many years because it's hard to accomplish everything in a single visit. And so this kind of longitudinal continuity of care between individuals who trust one another is -- for me, it's always been the kernel of being a physician. It's just so important.

>> Yeah, it's the thing I like the most of my job and I think that this is a topic area where the longitudinal relationship really shows it a strength for prostate cancer screening. There'll be the longitudinal discussions about whether to get screened but many of my patients once they're diagnosed with prostate cancer, they're coming to me and talking about their options on treatment. And I think it's a good way of kind of getting at some of those values and helping them to think about how they might use those values in deciding what's right for them.

>> Thanks, Alex. So I just want reiterate the clinical summary screening for prostate cancer, population men aged 55 to 69, the decision to be screened for prostate cancer should be an individual one, grade C. For men 70 years and older, do not screen for prostate cancer, grade D. Alex, I want to thank you. The task force has done a fabulous job in summarizing the evidence and coming up with what I think are [music] patient centered, patient oriented recommendations that will serve us well for many years to come.

>> Thank you very much, Howard.

>> Thanks for listening everyone. This is Howard Bauchner, Editor-In-Chief of JAMA

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