TITLE: SCREENING FOR EARLY DISEASE DETECTION: Not as Simple as it Seems

PRESENTER: Julie E. Buring, ScD

Slide 1: I am very pleased to be here today to be talking about screening for early disease detection and the fact that it's not as simple as it seems.

Slide 2: Just recently in May of 2012, the U.S. Preventive Services Taskforce final report said that most men of any age should not routinely get PSA Prostate Specific Antigen screening for early detection of prostate cancer. And they made that decision based on the review of 30 studies and said, does not save life leads to unnecessary anxiety, surgery and complications from treatment of slow-growing cancer that never would have become life-threatening.

And they concluded that the life-saving benefit was at best very small and offset by over diagnosis and overtreatment of non-lethal cancers.

Slide 3: Well, you can imagine that, that got a lot of reaction; people said that it was sparking controversy; men were left to wonder as the PSA test was disputed.

Slide 4: And the confusing thing about it was that it would seem that PSA screening for prostate cancer should be just as straightforward. It's a simple blood test, it has the right mechanism of measuring protein and blood that's produced by the prostate tissue, it's widely accepted and used, routinely given this over 75% of men in the United States over the age of 50, it is the most common way, PSA testing, the most common way that the diagnosis of prostate cancer is in fact triggered.

And it picks up prostate cancer long before the symptom, significantly increasing the number of prostate cancers diagnosed at very early stages. So you would think that treating prostate cancer earlier would lead to better prognosis, but does it, and can it be harmful, are there risks associated with it?

Slide 5: Well, PSA testing for prostate cancer really reflects and illustrates the conundrum of screening that there are conflicting emotions regarding screening for early disease detection, whether it be from a public side, the clinician's side, the insurer's side. On the positive side, screening intuitively holds such promise. How could early detection not be beneficial? How could we not offer and want to receive screening tests?

But on the negative side, the population data are not clear that screening itself has actually worked. For some cancers, yes, it has led to an increase in diagnosis, but it hasn't always led to a decrease in mortality. And there have been some cancers like stomach and cervical cancer, where the mortality has decreased but there is absolutely no way that could have been due to screening, because there is no screen for stomach cancer and the decline of cervical cancer happened before the screen was introduced.

Slide 6: So why is the effect of screening so difficult to evaluate? To understand that; we have to go back and understand first the principles of screening.

Slide 7: Screening for early disease detection is the application of a simple test to asymptomatic person in order to classify them as likely or unlikely to have a disease.

Slide 8: Screening that we're talking about now is not screening for the safety of others. This is screening were you a personal benefit on your own prognosis and the key words in that definition that we need to remember is that screening is searching for early asymptomatic disease.

Once the disease has symptoms you are out of the screening phase into a diagnosis due to clinical symptom. The assumption underneath screening and the real purpose for doing screening is that early detection asymptomatically will lead to a more favorable prognosis. In other words, the treatment given before symptoms develop will be more beneficial, than waiting till evidence of the disease comes forward.

Also remember that screening is not a diagnostic test; that screening classifies the person is likely or unlikely to have a certain disease, then you apply the diagnostic test.

Slide 9: For screening to be successful we need three things. We need a suitable disease, we need a suitable test and we need a suitable screening program.

Slide 10: Well, what are appropriate diseases for screening? First there are diseases with serious outcome, either in actuality like cancer, cardiovascular disease, a serious disease or a disease that is perceived to be serious by the community.

An appropriate disease for screening also requires that treatment given before symptoms develop is more beneficial, than treatment that's given after symptoms develop, in terms of morbidity and mortality. So diseases treated asymptomatically will be just as highly fatal or just as highly curable if you waited for symptoms to develop, then that disease would not be a good candidate for screening.

It is a good candidate if it makes a difference, if you treated before symptoms develop.

Slide 11: The other thing that's required for an appropriate disease for screening is that the prevalence of the detectable preclinical phase is high in the screen population. The period of time where the disease is asymptomatic, it's preclinical and we have a screening test that is able to detect it or pick it up. Now we'll talk about what that means in just one second. But a point I do want to make is you do not need all three of these to be an appropriate disease for screening. For example screening newborns

for phenylketonuria, doesn't have all three of the conditions, it is not a common outcome that's in born error of metabolism.

But on the other hand it has such serious consequences that can be avoided if the dietary modification begins at birth. It is considered to be something that we routinely screen for even though few babies will actually have it. So let's go back for a second and understand that detectable preclinical disease phase.

Slide 12: If we think about the natural history of the disease, at some point there is a biological onset of the disease, then at some point the disease may be detectable by screen. But we don't have screening all the time, so we probably won't pick it up at the time it becomes detectable. But at some point a screen will be done, so that's the next cut off. And then at some point if we waited and didn't do a screen, the disease would be diagnosed by symptoms, and then sometime after that the person would die.

The detectable preclinical phase is the preclinical phase prior to diagnosis which is detectable with the disease, it is detectable by screen. So it is the period of time bracketed between when it is detectable by screen, that's when it begins, to when it ends, when it is diagnosed by symptoms; that is the detectable preclinical phase.

Slide 13: So for screening of be successful we also need a suitable test.

Slide 14: And an appropriate screening test is one that is simple, it's inexpensive, it's easy to administer and it's acceptable to a large number of potential screenees. This is going to be given to a very wide number of people. We also need the test though to be valid and a valid test does what the test is supposed to do.

If you have the disease, the test should screen positive, and that means it's going to have high sensitivity. If you don't have the disease, then you want the screening test to test negative, you have high specificity of the disease.

So the test should do what it's supposed to do. If a person has the disease, the test should screen positive, if they don't, the test should screen negative.

Slide 15: And we can do that by actually calculating sensitivity and specificity. So for the screening test we can set up a 2x2 table where the result of the screening test is on one axis and the gold standard, whether the person actually has the disease or not, as evident by the diagnostic test will be on the other axis.

So A) will be the true positive. The person screens positive on the test, the screening test, and in fact, does have the disease. B) False positive, they tested positive on the screening test, but after the diagnostic test was done, they in fact were not found to have the disease. C) is false negative, the person tested negative on the screening test, but in fact did have the disease and the screening test missed it. And D) false negative, they tested negative on the screening test and in fact they did not have the disease.

The sensitivity will be the probability that the person test positive on the screening test, given that they actually do have the disease. The specificity is the probability the person test negative on the screening test, given that in fact they do not have the disease.

So the sensitivity will be a over a+c, out of all those who have a diagnostic test that's positive, they really do have the disease, a+c. a of them tested positive on the screening test sensitivity, and on the specificity out of all of those who do not have the disease b+d, the probability or the proportion of those who tested negative on the screening test d/b+d, the specificity.

Slide 16: So in fact, if we use data, and we use the data from the Health Insurance Plan of New York where the screening test was mammography plus physical exam and the outcome was breast cancer diagnosed through a biopsy. Well in this study there were 64,810 women who participated in the study. Of those 1,115 tested positive on the mammography, it was mammography plus physical exam. We will call it mammography.

And the other 63,695 women tested negative on the mammography. All the women who tested positive on the mammography went and had a breast biopsy. So, 1,115 women went on to have a breast biopsy. Of those biopsies, 132 women actually have breast cancer after the biopsy, and the remaining women 983 had a biopsy, but they were cancer free.

Now the 63,695 women who detected negative on the mammogram, 45 women were diagnosed with breast cancer by symptoms, by clinical symptoms within the next one year period of time. What we know about mammography is that it should advance the diagnosis of breast cancer by about a year.

So those 45 women were actually missed by the mammogram. They should have been able to be picked up. Now that's a very conservative statement, because there is no question that some of those women really did not have the disease when the mammogram was done, they just have a rapid very aggressive disease. It was not there to be picked up with the mammogram, but it became not only able to be picked up by a screen, but it was picked up by symptoms within a one year period of time.

But conservatively we're going to say the mammogram missed them. And the other 63,650 women had a negative mammogram and had no clinical evidence of breast cancer within the next one year period of time. So they are considered true negative. The sensitivity of the mammogram is a probability that the woman tested positive given that she has breast cancer, so that's 132 out of 177 or 75% and the specificity is the probability that she tested negative given that she did not have breast cancer. 63,650/64,633 or 98.5% and what this means is that screening was very good at identifying women who did not have cancer, specificity 98.5%, but missed 25% of women who did have cancer. So the sensitivity was only 75%.

Slide 17: Well, can we do anything about sensitivity and specificity? Can we modify them in some way? Well, it turns out that it's going to be dependant on the criterion of positivity. As we all know, some test results are going to be clearly negative, some test results are going to be clearly positive and there is going to be a gray zone in between, where at some point we are going to put down a line and say, everything below this is going to be negative and everything above this cutoff is going to be positive and that is the criterion of positivity, the test value at which the screening test outcome is considered to be positive.

Slide 18: Well by modifying the criterion of positivity, we can actually influence both the sensitivity and specificity of the screening test. So let's say that we are interested in screening for blood pressure and 140/90 is going to be the level that we really are going to want to detect when we talk about hypertension.

Well, let's say, we lower our criterion of positivity, let's say we are going to screen and pick up anybody whose blood pressure is 132/80, much lower than actually the value that we're looking for. By lowering that criterion of positivity, we are going to have a very sensitive test. We are going to pick up absolutely everybody who has hypertension, but there are going to be a lot of people we pick up by our screen who don't end up being hypertensive by our examination. So we are going to have a very much lower specificity, because there will be many people who are positive on our screen, but don't end up being diagnosed with hypertension.

If on the other hand we increase our criterion of positivity. Let's say we go to 160/105, we are going to lower our sensitivity, we are going to miss some hypertensive cases, but we are not going to send anybody through a diagnosis of hypertension without reason. All of those that we sent through are actually going to be hypertensive. So our sensitivity will have been lowered, but our specificity will have been increased. So that you can see that the sensitivity and the specificity are characteristics of the screening test, but they can be modified and traded off against each other.

We have to weigh the cost of a false positive. The cost of saying that someone might be hypertensive and sending them to their healthcare provider to go through a diagnostic test to figure out if they truly are hypertensive or not unnecessarily, against the cost of false-negative, reassuring someone that they do not have in fact breast cancer because their mammogram was normal or they do not have hypertension because their screen for hypertension was normal. And lulling them into a false sense of security based on our screening test, when in fact we are wrong and when in fact they actually do have a disease.

Slide 19: So we said, we needed a suitable disease, we said we needed a suitable test and now we need a suitable screening program.

Slide 20: And the evaluation of a screening program is going to have two components to it. It's going to have the component of feasibility, can we actually do the screening program and effectiveness. Let’s say, we can't do this screening program, does it matter if we do it, does it make a difference to prognosis if we do this screening program?

Slide 21: So the first thing we want to look at in our evaluation of z screening program is feasibility and feasibility as the number of components to it. First is simply acceptability. Are we delivering the screening program to the people that we wanted to deliver it to? So the acceptability of the screening tests to our potential screenees, and we usually measure that by the proportion of the target population who are screened.

So of those that we wanted to reach with our screening program, what is the proportion of that population that was actually screened, but it actually is going to turn out we have to do one more thing beyond that, we simply cannot just screen them and leave them then, with no ability to figure out whether they actually do have the disease or not, they actually need to go in and be diagnosed based on what their response was to our screening program.

So the second thing we want to look at is the success of follow-up, the proportion of those who test positive, who actually receive the diagnostic test and the treatment as indicated, those are two different things.

One of them is to make sure that we have setup an ability in our community for them to go somewhere and actually get a diagnostic test.

And then put them in a position where if treatment is necessary and if they want that treatment, that they can receive it, so the success of follow-up.

We also want to understand our cost and the cost-effectiveness of the screening program. The cost is very simple; we can just look at the total cost of the screening program. But many would argue it makes a difference, whether then you detect one case for that cost or you detect thousands of cases for that cost. So you can actually do a cost per case detected, which gives you a little bit more of a cost-effectiveness measure.

Related to that then is to understand our yield of the screening program. Meaning, how many who tested positive on the screen actually do have the disease after the diagnostic test has been done? So it's called the predictive value of a positive test. Now we can actually do a predictive value of a negative test also, but primarily people will look at the predictive value of a positive test.

Slide 22: The predictive value of a screening test is calculated in the following way: The predictive value positive is calculated by basically looking at the screening program the opposite way from the sensitivity and the specificity. Sensitivity and specificity were related to the test, so we wanted to know how well the test did. So we looked at among all those who have the disease, what proportion test positive against specificity, among all those who do not have the disease. How many test negative?

But in a predictive value we want to invert that and say if I test positive, if a patient test positive, what is the probability that they will actually be diagnosed with the disease once the diagnostic test is done. So predicted value positive would be the probability that the person has the disease given that they test positive, and the predicted value negative would be the probability that the person does not have the disease given that they test negative.

So predictive value positive and predictive value negative of course, will depend on the sensitivity and the specificity of the screening test. You need to have a good test for you to be able to predict whether you have the disease or not. But more importantly, they are going to depend on the prevalence of the detectable preclinical disease in the screen population. How common is the disease that you are screening for among the detectable preclinical phase of the disease in your population?

Slide 23: So if we back to our mammography in our breast cancer example, the predictive value positive will be of all of those who tested positive 1,115 what proportion of those actually have the disease after the biopsy was done? So 132/1150 or 12%, so that means that a woman who has a positive mammogram has 12% probability of going on to be diagnosed with breast cancer after her biopsy. And the predictive value of the negative test means, of all of those who tested negative on their screen, what probability have the disease negative when they are finished with the biopsy, they will be told they did not have breast cancer?

So that 63,650 out of 63,695 or 99.9%. Well, how can we change that predictive value positive? Basically, what we're saying here is in this particular screen only 12% of the women who were indicated to test positive on their screen actually do have breast cancers. Is there anything we can do about that? Well, we cannot do much to change sensitivity and specificity of the test, we talked about that

previously and it really is a characteristic of the test that we have available, but we can change the prevalence of the detectable preclinical phase. What does that mean? It means that we can target our screening test to a population that has more people in the population who are likely to have the outcome or the disease, so that we can basically screen a higher risk group.

So rather than screening for breast cancer among teenage girls who are unlikely to have breast cancer to a great degree, we can target our screening program to women over the age of 50 who have a family history of breast cancer, a personal history of benign breast disease, may be have a late age at first birth.

By doing a higher risk group, we will have more women in the detectable preclinical phase that will increase the prevalence in that phase and it will increase the predictive value positive of our screening test, and the other way to do it, is to do one screening test that is not that predictive. But then for those who tested positive, go ahead and simply give them a second screening test, so that basically we're building a second test on top of our first test.

Slide 24: So we now talked about how to look at the feasibility of a screening program. Now we need to look at the effectiveness of a screening program. And there are two ways that we can do that. We can look at early outcome measures and then we can look at a more definitive measure, which is going to be mortality.

So the early outcome measures mean, that we're picking up early disease, we just confirm that we are picking up early disease, if it's cancer for example, we want to demonstrate that we shifted the stage distribution of the disease to the left, which means we picked up more early stages of that cancer, which we would think would be less severe disease.

Well, that in itself is excellent to show that we are picking up early disease, it's almost necessary to show that, but what is the relationship with prognosis? We all know that even early stages of the disease can sometimes have a bad prognosis and sometimes late stages of the disease end up having a good prognosis. So we don't know the clear, it is not clear that having early stages of the disease picked up, means that we are necessarily going to have a better prognosis and necessarily going to save lives. There is not a one to one correlation there with that.

So what would be better for us to look at? Well, the very best thing and most definitive thing we can look at is to look at cost specific mortality rates, and look at these cost specific mortality rates and compare them for both the screens and the unscreened individuals.

Slide 25: But, when we do that though, there are going to be some special issues that we're going to need to look at. We can go ahead and actually look at the effectiveness to any epidemiologic designed strategy to a randomized clinical trial through an observation study, but there will be special issues in the evaluation of screening program that we will need to take into account, which is not relevant to other kinds of evaluations that we might be doing.

We are going to need to look at volunteer bias, if we are doing an observational study and we are going to need to look at lead time bias and length bias even if we're doing a randomized trial.

Slide 26: Volunteer bias just says that if you're doing an observational study and you're going to go ahead and look for people who volunteered to screen, versus people who did not volunteer to go

through a screening program. Basically, we are going to be comparing those who self select to be screened, versus those who self select to not go through a screening program. And it's going to turn out that those who volunteer for screening are going to be systematically different than non-volunteers, and they are going to be different in ways that are related to the outcome understudy. In other words, it's going to be confounding, simply because you volunteered to be in the screening program, you are going to be different than those who do not.

They could be healthier people; they could be people at higher risk of developing the outcome understudy. So they are more scared people. And so whether it goes one way or the other they have less risk factors or they have more risk factors, the fact is those who volunteer for screening are going to be different from those who do not, and we're going to need to take those variables into account when we look at their risk of developing the outcome understudy, like the development of the disease or more importantly the development, the survival of the disease, so the development of the disease, morbidity, mortality from the disease.

Slide 27: The other two are really unique to screening and the first is lead time bias. Lead time says that in every screening program you actually have advanced the diagnosis just because you did a screening test.

In other words these people are asymptomatic. On that day they had absolutely no symptoms of their disease. On that day they would have not come into their healthcare provider and said I have a symptom I need you to look at it and then they diagnosed the disease, because there were no symptoms.

So by picking up the disease by screening while the person is asymptomatic, you are advancing the diagnosis of the disease. So lead time represents the time between when the disease was diagnosed because of the screening test, and when the diagnosis would have occurred by clinical symptom. And with lead time bias, because by definition the diagnosis is always advanced by the screening program, cases that are detected by the screening may actually incorrectly appear to survive longer, only because of their earlier diagnosis.

In other words, they don't live any longer, but it looks like there is a longer time from diagnosis to death, which could be misinterpreted as having a longer survival.

Slide 28: So again, let's do a picture and then, do an example. We had talked about the biological onset of the disease, then the time when the disease could be detectable by screen, the time when you actually did screen for the disease and then the time when the diagnosis was made by symptoms, and finally, the time when the patient died. We talked about the detectable preclinical phase when the disease could have been detectable by screen, and then, when it was no longer able to be detectable by screen, because it was being diagnosed by symptom.

But there is now one more time, which is the time between when the screen was done and when the diagnosis was made by symptom and this is the lead time. This is the time by which the diagnosis is pulled forward from when it would have occurred by symptoms, because you actually did a screening test.

Slide 29: So let me give you an example of how we could be misled if we don't take that into account; that lead time. Let's say a randomized trial was conducted to evaluate the effectiveness of the new screening program for colon cancer. Among those whose cancers were detected by the screening program, their average age of diagnosis was 54 years and their average age of dead was 60. So the average survival from diagnosis to death was 6 years.

For those who were detected by clinical symptoms, their average age of diagnosis was 56 years, their average age of death was 60 years, thus their average survival from diagnosis to death was four years.

The investigator reported in the article that there was a statistically significant two year increase in survival from colon cancer associated with screening. As the question goes, what is wrong with this picture?

Slide 30: Well, what's wrong with this picture is that both groups, the screening group and the symptoms group, both died at age 60, so there was no increase in survival, what there was, was an increase in the time that the person knew that they have the cancer, and those who were picked up by screen as you can see on the diagram, were picked up at age 54, those who were picked up by symptoms, were picked up at age 56.

That two year period is the lead time by which the diagnosis by symptoms was advanced, because it was picked up by the screen. That needs to be taken into account in some way. It isn't that they lived longer, but they were aware of their diagnosis, they lived with the disease knowledge two years more than those with symptoms.

Now many can argue that that's useful, the person has more time to make plans, to sort of adjust to the disease, may be the treatment at the early stage is not quite debilitating as those when symptoms are developed. So all of those are good things, but it doesn't change the fact that the person lived no longer and that's something that people need to understand if that is true.

So the problem was that lead time bias was not taken into account. We should never use duration average survival from screen to death and from symptoms to death without taking lead time into account and the easiest way to do that is simply compare the age specific mortality rate, just the death rates from colon cancer at age 60, from those who are diagnosed by screen, versus those who are diagnosed by symptoms.

Slide 31: Now the last type of bias that we need to always think about is length bias, and length bias is a little hard to understand, but let me try to explain it intuitively before the definition. When we go out the very first time and we do a screening program, I very much think about it as putting a net in the water and just scooping up everybody who is existing with the disease out in our population at that point in time. There are going to be prevalent cases.

People who may have had the disease for years or decades or those who have just developed the disease, but it is going to be very much a mixture of those who have very advanced disease because they have had it for a very short period of time, it's very aggressive and those who have had the disease for decades and might therefore be thought they have a very 'benign' form of the disease, not as aggressive, which would have done just fine anyhow, even if you would never pick them up by the screening program.

So the length bias says that the initial screen will be overrepresented by disease that have a longer duration in the detectable preclinical phase, prevalent cases, which are usually less aggressive and have a better prognosis, compared to incident cases, where incident cases are the ones that have made the change over to symptoms to being picked up clinically.

Now we have to in some way take that into account, and it's very hard to do, the way that people try to do it is by looking at subsequent screening tests. So it's going to be the very worst at the very first screening test. After that you are just taking people who screened negative on the screen and repeating the screen maybe one year later, two years later or five years later, so they don't have as long a time to be sitting out there without clinical symptoms, so it reduces the over representation of people with long duration and that is why you will often see people citing length bias, but saying that on subsequent screen we still thought a benefit in survival among those whose disease was picked up by the screening program.

Slide 32: So in summary, what we have tried to do is basically just raise our awareness that the appropriateness of screening for disease control is just not always clear, we need an appropriate disease, we need an appropriate screening to have one that's valid, that has adequate appropriate sensitivity and specificity. We need to evaluate the screening program both with respect to its feasibility, looking at predictive value and its effectiveness, after we control for special types of confounding and bias.

Slide 33: And we will find that some diseases are considered to be good and some are considered to be not good candidates for screening, that are breast cancer, colon cancer, hypertension, glaucoma, disease like that are considered to be excellent candidates for screening programs, a serious disease where a valid screening test exists and early treatment has been shown to make a difference.

But then we will hear people say that ovarian cancers or pancreatic cancers are not good candidates for screening, and what is usually meant by that is that we in 2013 just do not have an adequate screening test currently available, that will advance the treatment far enough to make a difference in prognosis, if the disease, these cancers are picked up asymptomatically.

Is it really a flaw of our abilities to have a good screening test that it can advance the pickup of the disease, enough to make a difference in terms of prognosis if you started treatment asymptomatically rather than symptomatically? And now we come back in close with prostate, whether prostate and all this a good disease or not a good disease and why was that decision made?

Slide 34: Remember we said that PSA, Prostate Specific Antigens seems so attractive, that it would seem straightforward; it's a major cancer in men, so check off that it's serious disease.

It's a simple blood test that it's widely accepted in use and it picks up prostate cancer long before the symptoms. So it seems like we have an acceptable test and we have a screening test that's valid. There are significantly increased numbers of cancers that are diagnosed at very early stages.

So we sort of have that first part of effectiveness where we have sort of shifted the stage curve to the left, but then how about the second part? Is there a better prognosis? If we treat in the asymptomatic stage does this translate into a reduction in death rate and are there risks of the screening? And this is

the part that we just didn't really at first think was going to be an issue, but it turns out to be, for the following reasons:

Slide 35: The bottom line is that many randomized clinical trials have been done, but they have found the life-saving benefit of PSA screening 10 years after the diagnosis prostate cancer and the postulated reason is that many prostate cancers that are detected by a screen, by PSA screening are very slow growing and in fact, might never have caused problems, if they had not been diagnosed because of the screening, this is the length bias.

And even worse than that, many patients have said that the diagnostic biopsy plus the treatment surgery or radiation is actually worse than the disease itself. And what the real problem from our standpoint is, is we're not sure what PSA level actually signals cancer. So there are going to be many false alarms, and in fact, 13% of men who have regular PSA screening have at least one false PSA finding for every four screenings, and 6% of them will then have a biopsy for this false reading.

Slide 36: So biopsies can be painful and can cause serious complications, infections, bleeding, urinary complications, but the real problem beyond that is if you do diagnose the prostate cancer, what do we do, with sort of the commonly accepted standard of care is at this point? Well, it turns out standard of care, two options, Option one, is immediate surgery with radiation perhaps hormones. Option two is watchful waiting, active surveillance with periodic biopsies.

Well, 20% to 30% of those with surgery and radiation have adverse effects, including urinary incontinence, erectile dysfunction, impotence, stroke, death, to go to the most extreme ones, and watchful waiting has a problem with the quality of life issue that many patients say, I can't deal with living with a cancer that is not removed, just get it out.

Slide 37: And unfortunately we don't have a prostate screening test, PSA is not it, we do not have a prostate screening test that distinguishes a relatively harmless cancer that would continue on without developing into anything bad until the patient dies of something else like old age. We can't tell that ones from a bad cancer that is going to become a rapidly growing very aggressive; will in fact cause mortality.

So the question that the group looked at when they made their recommendation, is how beneficial is it to treat prostate cancer early when the majority are not going to die of this disease and we can't predict who will die of the disease and the diagnosis and treatment are going to cause morbidity in themselves.

Slide 38: So you have very many emotional reactions from individuals, from clinicians, from insurers, from the individuals when the recommendation came out that they could not recommend screening for all men, that they did not think it was a good risk benefit ratio, there were emotional reactions from individuals in terms of our denying them, a potentially lifesaving test.

Some clinicians will say actually I don't care whether this screening test saves lives or death, it's irrelevant, it picks up early disease and it brings people into the health-care system routinely for exams; that in itself is going to help us save lives. We all agree that this is going to have implications for what Medicare and private insurers are going to pay for; that new Federal Healthcare law is going to base coverage requirements on these types of recommendations.

What really is now the majority of clinicians are saying that none of these recommendations say that an individual can't have a screening test, for different men, with different risk factors and different histories, we will make different decisions, but the important change is that we will inform them of the pros and cons of the testing, for their different risk factor profiles.

Slide 39: So the message I think to us is just to raise our consciousness, that there are a trade-off of benefits and risks of screening that screening is complex and that screening is intuitively attractive, it can really be a double-edged sword and that we need to try to avoid our intuition and just conduct the next necessary randomized trials for us to evaluate that we need to look at the data when we're making a decision as to whether screening is a good thing or a not good thing, for a condition or a disease that is of interest to us.

Slide 40: Thank you very much!