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CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Evidence Development & Coverage
Advisory Committee

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Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland

Reported by:
Paul Gasparotti

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Panelists

Chairperson
Clifford Goodman, Ph.D.

Vice-Chair
Saty Satya-Murti, M.D., F.A.A.N.

Voting Members
Charles S. Carignan, M.D.
Roger Dmochowski, M.D.
Josef E. Fischer, M.D.
James M. Hevezi, Ph.D., FACR/FAAPM
Jeffrey G. Jarvik, M.D., M.P.H.
Roger D. Klein, M.D., J.D.
Barbara McNeil, M.D., Ph.D.
Curtis A. Mock, M.D., M.B.A.
Louis Potters, M.D., FACR
David J. Samson, M.S.
Sanford J. Schwartz, M.D.
Robert L. Steinbrook, M.D.
Craig Umscheid, M.D., M.S.C.E.

Industry Representative
G. Gregory Raab, Ph.D.

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Panelists (Continued)

CMS Liaison
Marcel Salive, M.D.

Executive Secretary
Maria A. Ellis

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PANEL PROCEEDINGS

(The meeting was called to order at 8:10 a.m., Wednesday, April 21, 2010.)

MS. ELLIS: Good morning and welcome,

committee chairperson, vice chairperson, members and guests. I am Maria Ellis, the executive secretary for the Medicare Evidence Development and Coverage Committee, MedCAC. The committee is here today to discuss the evidence, hear presentations and public comment, and make recommendations concerning the currently available evidence regarding the risks, benefits and outcomes of radiation therapy inclusive of external beam radiotherapy and brachytherapy for the treatment of localized prostate cancer. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. Each member will be asked to disclose any financial conflicts of interest during their

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introduction. We ask in the interest of fairness that all persons making statements or presentations also disclose any stock or any other form of financial interest in any company, including Internet or E-commerce organizations, that develops, manufactures, distributes and/or markets devices or services, hardware, implants, surgical instruments, radiotherapy equipment, kits or testing equipment used for the diagnosis and/or treatment of prostate cancer. This includes direct financial investments, consulting fees, and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of this room. We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight agenda, and therefore cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please note that there is a chair for the next speaker, and

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please proceed to that chair when it is your turn. We ask that all speakers addressing the panel please speak directly into the mike and state your name. For the record, the voting members present for today's meeting are: Dr. Saty

Satya-Murti, Dr. Charles Carignan, Dr. Roger Dmochowski, Dr. Joseph Fischer, Dr. James Hevezi, Dr. Jeffrey Jarvik, Dr. Roger Klein, Dr. Barbara McNeil, Dr. Curtis Mock, Dr. Louis Potters, David Samson, Dr. Sanford Schwartz, Dr. Robert Steinbrook, and Dr. Craig Umscheid. A quorum is present and no one has been recused because of conflicts of interest. The entire panel, including nonvoting members, will participate in the voting. The voting scores will be available on our website following the meeting. Two averages will be calculated, one for voting members and one for the entire panel. I ask that all panel members please speak directly into the mikes, and you may have to move the mikes since we may have to share.

There is a TV network broadcasting and recording today's MedCAC meeting. This is in

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addition to the CMS Webinar and transcriptionist. By your attendance you are giving consent to the use and distribution of your name, likeliness and voice during the meeting. You are also giving consent to the use and distribution of any personally identifiable information that you or others may disclose about you during today's meeting. Please do not disclose any personal health information.

If you require a taxicab, there is a signup sheet at the desk outside of the auditorium. Please submit your name during the lunch break.

Please remember to discard your trash in the trash cans located outside of this room.

And lastly, all CMS guests attending today's meeting are only permitted in the following areas of CMS single site: The main lobby, the auditorium, the lower level lobby and the cafeteria. Any persons found in any area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.

And now, I would like to turn the

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meeting over to Dr. Barry Straube.

DR. STRAUBE: Thank you, Maria, and thank you Dr. Goodman and Dr. Satya-Murti for chairing and cochairing the committee today. I want to welcome everybody. I'm Barry Straube, I'm the chief medical officer here at the Centers for Medicare and Medicare Services, as well as being the director of the Office of

Clinical Standards and Quality, and I want to welcome our panel yet again. I am always amazed when I look over the hundred people who serve on the MedCAC panel from which we can draw, and then when we actually ask people and they agree to serve on these panels, it's always a very large group of renowned and respected individuals who have great subject expertise in the areas that we're delving into, so I want to thank all of you for taking the time to serve on this very important panel.

The MedCAC, as evidenced by our changing the title from MCAC, Medicare Coverage Advisory Committee, to MedCAC, Medicare Evidence Development and Coverage Advisory Committee has been evolving under Dr. Goodman's

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tutelage here of running this panel, and I think we're getting more and more focused on the need for the strength of evidence as we make coverage decisions here at CMS, particularly the strength of that evidence in the population that we cover.

As you know, many of the areas that we look at when we look at the evidence for general populations, the strength may be there, but we are more and more looking and challenging ourselves to see whether the evidence is applicable to our population, particularly those over 65, those with end stage renal disease and those with disabilities.

This particular topic is very timely and certainly relevant to that population of people. I think that as a sign of the need for this MedCAC, I was meeting with an academic department of urology a few weeks ago about other issues, but I happened to raise this issue to the diverse staff that was present that particular day, and I thought I was going to have to mediate a fist fight because there was a very decided and rather wide divergent

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opinions among that collegial staff on what they felt about best treatments for localized prostate cancer with radiation. So I'm very interested and the Agency is very interested in the deliberations today and we look forward to the advice that this panel will be giving us going forward.

So Dr. Goodman, I will turn it over to you.

DR. GOODMAN: Thank you very much, Dr.

Straube.
We have today just until 4:30 for an ambitious agenda on a topic with considerable potential impact on the wellbeing of Medicare beneficiaries. With that in mind, we do expect that all of our speakers, those providing public comments, and any who provide open public comments later on today, as well as my fellow MedCAC members, will be on point and concise today.
Do speak into the microphone. If you don't do that, we won't hear you, and just as important, our trusty court reporter won't hear you, which means that the important thing that you have to say will not get into the record.

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We have today a time schedule for public comments, I understand that there are a dozen such comments, each of which has been allocated by CMS a maximum of seven minutes. And because of our tight agenda today, including the need to hear from all of our speakers and to provide full discussion for this important subject, we will need to adhere to those seven-minute limits, and I and our cochair, Dr. Satya-Murti, kindly, though firmly, suggest that each scheduled speaker think now, think now about how to focus your comments in those seven minutes on the information that pertains directly to today's voting questions. Please focus on those if you can.
If you plan to present material that you soon find to be repetitive of previous speakers or that is merely background information in those comments about your organization, for example, you might consider dispensing with that material and focusing instead on those questions for today. In any case, please do heed the traffic light system and do know that we will proceed to the next

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speaker once you've used your allotted seven minutes. Thanks for that.
With regard to disclosures and introductions, I'm Cliff Goodman, vice president of The Lewin Group. Lewin is one of multiple subsidiaries of Ingenix, a health care information and analytics firm. Ingenix in turn is one of multiple subsidiaries of United Health Group, and another subsidiary of United Health Group is United Health Care.
With regard to interests, I understand that I have a mutual fund with some health care

holdings that could involve some of these issues. I have no other financial interests pertaining to today's topic. Dr. Satya-Murti.
DR. SATYA-MURTI: Saty Satya-Murti. I am a neurologist and I had been a contract medical director for a number of years, and I consult for industry, academic societies, and at MedCAC here as well. I once did consult for advanced prostate carcinoma treatment, it had nothing to do with the radiation end and the product is not on the market, and it was for late stage prostate carcinoma. No other conflicts.

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DR. GOODMAN: In any case, if you would recite your name and if you have any conflicts of interest, and if none, state none. Next.
DR. CARIGNAN: I'm Dr. Charles Carignan. I'm currently the CEO of NinePoint Medical and I have no conflicts.
DR. FISCHER: Joe Fischer. I'm a surgeon at Harvard Medical School and I have no conflict of interest that I'm aware of.
DR. HEVEZI: I'm James Hevezi, director of medical physics at the CyberKnife Center in Miami, and I am a consultant to Accuray Corporation.
DR. JARVIK: I'm Jeffrey Jarvik, a radiologist at the University of Washington. I have no direct conflicts of interest.
DR. KLEIN: Roger Klein, medical director of Molecular Oncology and BloodCenter of Wisconsin, and I have no conflicts.
DR. MCNEIL: Barbara McNeil, Harvard Medical School and the Brigham and Women's Hospital. No conflicts.
DR. MOCK: Curtis Mock, family medicine and geriatrics, medical director of

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United Health Care. No known conflicts of interest.
DR. POTTERS: I'm Louis Potters, I'm chairman of radiation medicine, North Shore LIJ. It's an academic department and I have no ownership in any of the equipment that we use, and have no other conflicts.
MR. SAMSON: David Samson. I'm director of the comparative effectiveness research at the Blue Cross and Blue Shield Association. I have no conflicts.
DR. SCHWARTZ: Sandy Schwartz, University of Pennsylvania. I own stock in General Electric and I have served as a

consultant to Genentech and a Blue Cross Blue Shield advisory committee.
DR. STEINBROOK: Robert Steinbrook, Dartmouth Medical School. No conflicts.
DR. UMSCHEID: I'm Craig Umscheid, I'm an internist and epidemiologist at the University of Pennsylvania, and I direct the Center for Evidence-Based Practice at Penn, and I have no financial conflicts of interest.
DR. RAAB: I'm Greg Raab, I'm an independent consultant, and I've provided

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consulting services to some companies who have product interests in this area. That includes Siemens and C.R. Barnes.
DR. GOODMAN: Thank you all very much. I believe we will proceed now to the CMS presentation and voting questions, Dr. Salive first.
DR. SALIVE: Good morning. I'm Dr. Marcel Salive and I am the division director here at the Coverage and Analysis Group here at CMS, and I want to welcome everyone to the panel and thank all the panel members for serving your very important role.
Today we're going to be discussing radiation-based treatments for localized prostate cancer, and we will present our questions this morning and hear from the technology assessment we commissioned, and we have a number of questions for the panel to analyze.
As you see, we have narrowed this topic a little bit into radiation-based treatments for localized prostate cancer. That is because it is a very complicated topic, the treatment of prostate cancer, and so we wanted

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to focus in on these modalities today. And I want to thank Deirdre O'Connor and the whole team for their efforts in preparing this MedCAC, and Maria Ellis.
DR. GOODMAN: Ms. O'Connor.
MS. O'CONNOR: I'm Deirdre O'Connor and I have no conflicts to disclose. Welcome to our MedCAC.
The voting and discussion questions are questions that identify for the panel the issues of most interest to CMS. The voting questions have a scale of level of confidence, one being the lowest and no confidence, and five representing a high level of confidence.
For the purpose of questions one through four, the outcomes of interest are

defined as mortality, survival and death rate; functional outcomes, erectile dysfunction, urinary incontinence, fecal incontinence; adverse events, rectal fistula, radiation burns, infection.

For question 1, how confident are you that there is adequate evidence to determine if radiation therapy for the treatment of localized prostate cancer affects each of the

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following health outcomes? Mortality, functional outcomes, adverse events.

Number 2. How confident are you that the evidence is adequate to conclude that the use of external beam radiation therapy improves each of the health outcomes listed below as compared to therapeutic strategy of watchful waiting? Again, mortality, functional outcomes and adverse events.

Number 3. How confident are you that the evidence is adequate to conclude that the use of brachytherapy improves each of the health outcomes listed below as compared to a therapeutic strategy of watchful waiting?

Number 4. How confident are you that the evidence is adequate to conclude that the use of each of the modalities identified below improves each of the health outcomes listed over the identified comparator?

4.a. Stereotactic body radiation therapy, SBRT including CyberKnife therapy, compared to classically fractionated external beam radiation therapy, EBRT, including 3-D conformal radiation therapy, intensity modulated radiation therapy and particle

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therapy.

4.b. SBRT compared to high dose rate brachytherapy.

4.c. SBRT compared to low dose rate brachytherapy.

Number 5. How confident are you that these conclusions are generalizable to, A, the Medicare patient population, and B, community-based settings?

We have two discussion questions.

Number 6. What type of additional evidence on the impact of radiotherapy on prostate cancer outcomes is needed to improve decision-making in the approach to treating localized prostate cancer?

And the last one, how can the medical research and provider community address the evidentiary gaps that may contribute to health

disparities that exist in the diagnosis, treatment and outcomes for localized prostate cancer?
Thank you.
DR. GOODMAN: Thank you, Ms. O'Connor. Following the identification of the questions for today's consideration, we will proceed to

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the presentation of the technology assessment. This was prepared at the Evidence-Based Practice Center at Tufts Medical Center. Presenting for that team will be Doctors Tom Dvorak, Stanley Ip, and Bannuru, again from Tufts.
For those of you that aren't familiar with this, the evidence-based practice centers are under contract to the Agency for Healthcare Research and Quality to conduct evidence reports and technology assessments, typically using systematic review methods. These reports are requested and are used by CMS as well as other federal agencies.
Dr. Dvorak, thank you for being here, sir.
DR. DVORAK: Thank you for the invitation. I have no disclosures. I am a radiation oncologist at Tufts and I have been asked by the team to help with some of the technical information.
So today we are presenting our report on the comparative evaluation of radiation treatments for clinically localized prostate cancer. This is an update of a previous report

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by the Minnesota EPC that reviewed all the treatment modalities, not just radiation therapy. And this is a draft that has not been peer reviewed yet due to the tight time line.
I will present some background information on prostate cancer, some of the management options, we will review the Minnesota report highlights, and then we will present to you our findings.
Prostate cancer is a large public health problem. It's the number one cancer diagnosis for men and number two cause of death for men for cancer. Median age at diagnosis is 68 years old, although it's important to bear in mind that already by the time one is 40 years old, about 30 percent of men may have prostate cancer on autopsy in healthy men.
Lifetime risk of carrying the diagnosis now is about 16 percent, although this depends on how hard one looks. Before PSA

screening, this was about half, and obviously if you biopsied everyone this rate would be quite a bit higher. The risk of death, about three percent lifetime. The diagnosis can be either clinically by routine visual or rectal

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examination or by PSA screening. There is now a significant controversy about the guidelines and the screening that results in a biopsy. It's important to understand the anatomy. The prostate lives underneath the bladder in front of the rectum sort of behind the pubis, and these relations can give rise to the toxicity or the risk of treatment, including radiation therapy, so we will be talking about genitourinary toxicity, gastrointestinal toxicity, sexual dysfunction, and the risk of secondary malignancies. The cancer itself, the cancer grade is determined by a Gleason score which ranges from one to five, five being the most aggressive, although clinically it's really grades three, four and five that are used now. The Gleason score is a sum of the primary and the secondary patterns for a total score of two through ten. In terms of staging, stage one is disease which is clinically inapparent, you cannot palpate it, you cannot see it on imaging, so it's typically picked up by PSA screening, Disease T2 is confined within the prostate, and these two are part of the EPC

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report that we have been asked to present today. In terms of prevalence, the vast majority of patients now have either T1 or T2 disease. It's important to understand the natural course of the disease when we are talking about treatment outcomes. For men who were clinically diagnosed before the PSA era for whom we have sufficient follow-up, about ten percent of them are alive after 20 years, and of these, more than half do not die of prostate cancer, they will die of other causes. Of course the flip side is also true, that somewhere between a third and a half do die of prostate cancer. With PSA screening there are some estimates that it pushes back the clinical course by ten to 12 years from the time of PSA diagnosis to actual development of clinical disease. Now there is a variance in that some men do die of prostate cancer, some don't, so one of the studies looked at the variable

prognosis and some men, depending on what their grade is, for example if they're older, if they have low grade disease, their risk of dying

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from prostate cancer is minimal. On the other hand, other men, if they are younger with a high grade disease, their risk of dying from prostate cancer is quite high, and so the question is who should be treated and who should not be treated.

There is very good evidence, which is not part of our report, that young men with high risk cancer have a survival benefit with radiation therapy, this is from a local advanced setting, which is why it is not included here. So there are different ways of stratifying patients based on the P stage, the PSA and the Gleason score. This is one NCCN guideline staging such that patients are separated to very low risk, low risk, intermediate risk or high risk, and then depending on their risk factors they are offered several different treatment options, either no initial treatment, of which there are several forms, radiation therapy, or radical prostatectomy.

Key question one for our report relates to the evidence of no initial treatment versus radiation therapy comparisons. Key

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questions two and three then look at the specific radiation therapy itself.

Just a quick overview. Radiation therapy, there are rays that kill cells by damaging the DNA. They can be either photons, which are x-rays essentially, or they can be particle therapy such as protons. They damage everything in their path, including the tumor and the surrounding normal tissues. And the different tissues that we discussed previously respond to radiation in different ways.

Fundamentally there is two different types of radiation delivery, either from outside of the patient or implanted directly into the patient. For the purposes of our report we have separated out external beam radiation therapy and stereotactic body radiation therapy, SBRT, and we will discuss the distinction between these two. And then brachytherapy can be added either permanently as a low dose rate implant or temporarily as a high dose rate implant.

This is what we see. As you can notice, you don't really see where the prostate

is or the surrounding organs, and so this
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brings up the key question of efficacy versus toxicity for radiation. We try to treat the target and at the same time attempt to avoid the surrounding tissues, which is the major focus of the advances in radiation therapy. This is sort of the historical perspective, bladder, rectum, and the prostate is somewhere within that area. With introduction of CT scanning we can much better see where the prostate is in three dimensions, or maybe even using MRIs, and that allows a much more precise determination of where the prostate is, where the rectum is, and where the bladders are, which are the main organs for toxicity. This is just a comparison to the previous.
Of course a big problem is that the prostate moves and moves quite a bit. Radiation, external beam radiation is delivered Monday through Friday over seven to eight weeks, and here you can see for example shifts from day to day that can be up to a centimeter, so that if we make our radiation field margins too tight, we run the risk of missing the prostate. There is also significant motion
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during treatment, here you can see about 12 minutes worth, and a couple minutes into it you can see about a one-and-a-half-centimeter spike, and then the prostate keeps moving because of bladder and rectal filling. There's different strategies of managing the motion both in terms of between treatments and during treatment, which include daily imaging, different forms of immobilization, as well as realtime imaging, either electromagnetically or using x-rays.
And finally, brachytherapy avoids the motion problem altogether by implanting the radiation directly into the prostate.
There is a real clinical impact of this, and this is a landmark study out of M.D. Anderson Cancer Center where they looked at patients who under initial treatment plan had a big air pocket in their rectum. You can see that the prostate is sort of sitting up front with a high dose radiation field around. And as you imagine over the next seven or eight weeks, if that air pocket is not there, the prostate springs back outside of the high dose field, and there's a real clinical impact in
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that the patients who didn't have the air pocket had about a ten percent failure rate, the patients who did have the air pocket had about 40 percent, so there's a real clinical impact on missing the target. On the other hand, the toxicity because the rectum was also out of the way was much less.

So now that we know where the prostate is, how do we get the radiation there? Intensity modulation allows to preferentially give parts of radiation to different parts of the beam as the beams are coming from different parts of the patient such that the prostate itself receives the high volume radiation, high dose radiation, and the rectum not so much.

CyberKnife technology takes us in a way one step further, and targets hundreds of little beams across different parts of the prostate such that you can then very precisely deliver the radiation into the prostate, spare the bladder and spare the rectum.

Finally, the role of proton therapy. If you look at the classical x-ray therapy, each beam which comes from the patient, most of

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the dose is deposited within the first couple centimeters, so it's sort of shallowed by the skin, and it's really the summary of all these beams that then get the high dose regions. Proton therapy, on the other hand, most of the dose is deposited directly into the tumor, not as much front or behind, and so that allows a similar high dose region but much more sparing of the low dose regions.

Once we know where and how to give the radiation, the question is how much should we give, the dose. Typically radiation is given at 1.8 to two gray, which is the unit of radiation, per day, these are the maximum up here. And of course one of the questions is what is the dose necessary to treat prostate cancer. This is complicated by the fact that if you give more than the standard two gray per day, the damage to the cells is exponentially higher, and so with this there is a concept of biologic effective dose, which is essentially the total dose that you're giving, the physical dose, multiplied by a conversion factor. This conversion factor depends both on the dose per day or the dose per treatment you're giving, as

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well as the radiobiology, the response of the tissue to radiation and how well it can repair

the DNA damage, this is represented by the alpha-beta ratio.

So that if for example we give 80 gray in two-gray fractions over 40 days, we might get 130 biological dose. If we give the same 80 gray at ten gray for eight treatments, the biological effective dose is about two-and-a-half times as high.

The reason this is important for prostate cancer treatment is that there are different schedules that have been published. These are the two common ones here, given over eight to nine weeks. This would be the schedule that would be given by the stereotactic body radiation therapy approaches, and you can see that if you calculate the tumor dose, it may be that the SBRT dose is a little bit higher and the rectal dose is a little bit lower, but this critically depends on the alpha-beta ratio and the assumption of these calculations. If you use different alpha-beta ratios it may be that the dose is lower ten or 20 percent, and the rectal dose may be higher.

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This is one of the areas that is currently under research.

So in summary, the evolution of radiation therapy from 2-D to 3-D, from IMRT to SBRT is a function of the technology advancement. SBRT then requires CT planning, intensity modulated beams, daily imaging, stereotactic immobilization, and few large dose fractions.

This is what a modern setup would look like, this is at Tufts. The beam comes from here, there's a CAT scan on board, the patient is immobilized, and there can be image guidance also to account for respiratory motion.

Now in terms of brachytherapy, this is an operative procedure. While the patient is in the OR, there is a number of needles that get placed through a template and then radioactive sources are implanted directly into the prostate and they give off radiation locally.

The key questions here are which source, which radionuclide do we use. There are different energies which determine how far the radiation will penetrate and different half-lifes as to how quickly the dose is deposited. And again,

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the question is what cumulative dose should be used.

In terms of high dose rate brachytherapy, a similar concept where

catheters are implanted directly into the prostate gland. These are hollow catheters. The patient is then brought to the radiation department and from the outside a radioactive source is inserted into these catheters. There is typically one radionuclide used at one source and the question of dose schedule here is critical because this is an implant, it requires hospitalization, and typically these are much abbreviated fractions, called large dose per day.

In terms of the treatment evaluation, there's both clinical outcomes as well as biochemical outcomes by monitoring PSA. The PSA failure is now defined as the lowest point after treatment plus two. So as you can see here in a hypothetical patient, the PSA drops down, then it can rise up a little bit again, it goes down again, and eventually starts rising, and it's really when it reaches the two that we consider this to be a failure.

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And then there is the toxicity and quality of life outcomes of some of the surrounding organs that we discussed earlier. Many of the reports that we will be presenting to you used the RPOG grades, and a grade three toxicity is commonly reported. For example, for the GI this would be bloody discharge requiring sanitary pads, for the GU, genitourinary toxicity, this might be urgency or frequency on an hourly basis or frequent use of narcotics.

Now, our report is an update of the previous report by Minnesota EPC which looked at all different treatments through 2007, and their main findings really were that no one therapy can be considered the preferred treatment, and this was partly due to the limitations in the body of evidence and partly due to the tradeoffs between the effectiveness and the adverse effects of different treatment modalities. All treatment options result in adverse effects, and no trials enrolled patients with PSA detected disease.

For our report, there were no randomized trials comparing external beam

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radiation with watchful waiting. Further, no external beam regimens were found to be superior. There were no randomized trials comparing some of the other treatment modalities. One trial showed a decrease disease recurrence in radical prostatectomy

compared with external beam radiation therapy, this is an older smaller trial, and one trial found a decrease in disease-specific mortality in radical prostatectomy compared to watchful waiting. In one trial it was not significant.

DR. GOODMAN: Dr. Dvorak, please, two things. Can you go to the previous slide for just a moment, and can you slow down by about 7.4 percent?

DR. DVORAK: Absolutely. The main finding here is that no one therapy could be considered to be the preferred treatment, and this was because of the limitations in the evidence itself, as well as the fact that there are tradeoffs between the outcomes and the side effects, and these tradeoffs sometimes depend on the individual patients. The conclusion also was that all treatment options do result in side effects, which has to be borne in mind.

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No trial enrolled patients with PSA detected disease, so as you remember, most men today are in fact diagnosed with PSA detected disease. And there are no randomized trial comparing external beam radiation therapy to watchful waiting.

Would you want me to go over this one as well?

DR. GOODMAN: Proceed, but at the same pace, thank you.

DR. DVORAK: So no external beam radiation therapy regimen, but they looked at conventional radiation, high dose radiation, hypofractionated regimens were found to be superior in reducing mortality outcomes. A frequent outcome is biochemical progression-free survival, which is the PSA, but in terms of mortality there was no difference.

There were no trials that looked at brachytherapy, prior therapy, robotic-assisted prostatectomy, primary androgen deprivation, proton beams or IMRT, so any of the modern treatment options.

One trial found a decrease in disease recurrence, so a better outcome in radical

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prostatectomy compared to external beam radiation therapy. This was again an older trial, before all the technology advancements that we discussed. And one trial found a decrease in disease-specific mortality, so again better outcome, in radical prostatectomy compared to watchful waiting. A second similar trial was not significant.

So now, Dr. Ip will be presenting our evidence. Thank you.
DR. GOODMAN: Thank you.
DR. IP: Good morning. I have no conflicts of interest.
I will be talking about the methods that we used to conduct the review. Basically we asked the following three key questions in our report. Number one, what are the benefits and harms of radiation therapy for clinically localized prostate cancer compared to no treatment, or no initial treatment in terms of clinical outcomes?
Number two, what are the benefits and harms of different forms of radiation therapy for clinically localized prostate cancer in clinical outcomes?

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And number three, how do specific patient characteristics affect the outcomes of these different forms of radiation therapy?
The population that we're interested in are men with clinically localized prostate cancer T1 T2 staged disease, regardless of how old they are, what their histological grades were, or what their PSA concentrations were.
The interventions of interest are the ones that Dr. Dvorak talked about earlier. We also are interested in no treatment or no initial treatment. In our report, watchful waiting, active surveillance or observation, they are all considered equivalent.
Many of the studies in our report, they enrolled patients who had some forms of hormonal or androgen deprivation therapy. We included them unless the study's specific objectives were to evaluate whether or not hormonal therapy with radiation therapy makes a difference.
The outcomes of interest are overall and disease-specific survival, biochemical progression-free survival, quality of life including bowel, bladder and sexual

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dysfunction, and other adverse events like second primary cancer.
The kinds of studies that we were primarily interested in are comparative studies, i.e., randomized controlled trials or nonrandomized comparative studies. All the single cohort studies that had before-after analysis, we excluded them. This is a figure showing the kinds of studies we included.
Basically we have two sources. One source is

from the MEDLINE, that we did the search in the last two years. The other source is the nine randomized controlled trials in the Minnesota report that's related to radiation therapy. We decided to also include that in our analysis and we have a total of 62 studies. The reason we did that is because between the time of the Minnesota report and our report, EPC-wide we have tried to standardize the way that we evaluate studies. So their method is a little different from ours, so it's safer that we just look at the studies ourselves. So we used the AHRQ comparative effectiveness review methods guide and we rated individual quality of the studies using three

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grades, A, B and C. We also rated the strength of evidence for each of the key questions. It should be noted that strength of evidence is specifically pertaining to the studies that we have reviewed in these last two years. And we take into account the number and quality of the primary studies, the study design, duration of follow-up, consistency of the results across studies, and the ratings are segregated into three levels, high, moderate or insufficient. It's insufficient if the evidence is unavailable, limited, or if the results are inconsistent or if they are C quality studies. This is an overview of the kinds of studies that we have in our report. On this slide you can see the different kinds of comparisons and up here are the different kinds of outcomes, patient survival, biochemical failure or toxicity. Within each row, the first row are the studies, randomized controlled trial, prospective cohort, retrospective cohort, the size of the circle is proportionate to the sample size. And the main message from this slide is there are really no studies that examined or reported patient

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survival.
Dr. Bannuru will now come up and discuss the results of key questions one and two, and then I will come back and up and wrap up the report.
DR. GOODMAN: Dr. Bannuru.
DR. BANNURU: Thank you. I don't have any conflicts of interest, and I will be discussing the key question one and two. Our key question one is, what are the benefits and harms of radiation therapy for clinically localized prostate cancer compared

to no treatment or no initial treatment in terms of clinical outcomes? For this question we have five studies and all of them are retrospective studies, of which two of them used registry data.
And coming to this slide, during this presentation I will be using this kind of graph, so first I would like to go over it.
So, this is the line of no difference and this square here represents the effect size of each study, and this horizontal line represents nine separate confidence intervals, and when this confidence interval crosses the line of no

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difference, then there's evidence statistically not significant, and our x axis would be the outcome metric, for example on this slide it is hazard ratio. It is important to note that this is just a graphical representation of the results and we are not reporting any summary results.
DR. GOODMAN: Dr. Bannuru, I'm sorry. You say three retrospective cohorts, and I think I see four studies.
DR. BANNURU: Don't worry, I'm going to explain that. You're one step ahead of me. Coming to this particular slide, there are three studies, and four analyses have looked at patients for radiation therapy versus no therapy or no initial treatment. Of these, three studies found no differences and only one analysis has found increased patient survival with radiation therapy. The strength of evidence for this outcome is insufficient.
DR. SCHWARTZ: Excuse me, can you go back? Can you just explain? The point estimates look like there's a reduced risk, and there's just a tail of the confidence intervals that go above one?

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DR. GOODMAN: Dr. Schwartz, let's hold these questions until the presentation is finished and then we'll get them all at once. Thank you. Please proceed.
DR. BANNURU: So in terms of genitourinary toxicity, one retrospective study which analyzed data with this database has reported no difference in toxicity with brachytherapy alone or with external beam radiation therapy alone, but it reported an increased toxicity with combination therapy.
Now let's look at the patient survival, I think I went by -- I'm sorry. Okay. With a second primary cancer, one study

analyzed a data registry and found no difference with brachytherapy but they found increased toxicity with external beam, increased second primary cancer with external beam radiation therapy.

Now let's move on to key question two, what are the benefits and harms of different forms of radiation therapy for clinically localized prostate cancer in terms of clinical outcomes? For this question we have seven comparisons. The top four are between modality

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comparisons and the bottom three are within modality comparisons.

Our first comparison in this group, or for this question is stereotactic body radiation therapy including CyberKnife, and we found no acceptable studies for this comparison.

Our next comparison for this key question is low dose brachytherapy versus external beam radiation therapy. There are six studies which reported freedom from biochemical failure. All of them are retrospective studies and thus, because androgen deprivation therapy interacts with radiation therapy, we decided to divide this into two different groups based on whether the drugs are included, patients receiving androgen deprivation therapy. So in the group with patients receiving androgen deprivation therapy, three out of four trials reported increased freedom from biochemical failure with low dose brachytherapy, and in the other group there's no difference, and the strength of evidence for this outcome is insufficient.

In terms of disease-specific

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mortality, one retrospective cohort study reported no difference.

In terms of genitourinary toxicity, there are four prospective and two retrospective studies reporting this outcome. In the prospective studies they used different disease-specific quality of life scales and reported varying results. The two retrospective studies reported no difference in acute genitourinary toxicity and reported increase in, decreased toxicity with external beam radiation therapy. With respect to genitourinary outcomes, the strength of evidence is insufficient.

One study analyzed a serial database and looked at bladder cancer incidence and it

reported decreased bladder cancer incidence with low dose brachytherapy. In terms of gastrointestinal toxicity, four prospective studies and three retrospective studies looked at this outcome. Turning to prospective studies, they used different disease-specific quality of life scales and they reported varying results. Coming to the retrospective studies, they used

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RTOG scales and reported no difference in GI toxicity, and the strength of evidence for this outcome is insufficient. The same study which looked at bladder cancer incidence has also looked at rectal cancer incidence and found a decrease in rectal cancer incidence with low dose brachytherapy. Our next outcome of interest is sexual dysfunction, and the four prospective studies that have look at it have used different scales and reported varying results, and the strength of evidence for this outcome is insufficient. The next comparison we will be looking at is high dose brachytherapy versus low dose brachytherapy, and we have identified only one individual study for this outcome, for this comparison, and it reported no difference in biochemical control. It also reported genitourinary and gastrointestinal toxicity but without reporting the P values, but our calibrations showed that there is no difference in GI toxicity but an increase in genitourinary toxicity with low dose brachytherapy. In terms of sexual dysfunction, the same study reported no difference.

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And we also looked at combination therapies. There are six different combinations, each of them combining various forms of brachytherapy. There are over ten studies but only three had clinical results for this comparison. The two retrospective studies reported genitourinary outcomes, and the first one reported increased genitourinary toxicity with combination therapy and the other one reported increase in urethral strictures with combination therapy, and the strength of evidence for this outcome is insufficient. And one retrospective cohort analyzed a serial database and looked at second primary cancer and they reported increased second primary cancer in the combination therapy group. Next we looked at within modality

comparisons, and the first one in this group would be intra-stereotactic body radiation therapy. We found one study looking at genitourinary and gastrointestinal toxicity and this study used about 300 patients, of which 50 of them received 35 gray and the other 250 of them received 36.25 gray, and they reported no

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difference in the genitourinary or gastrointestinal toxicity.

And the next comparison of interest is intra-external beam radiation therapy, and it's related to dose comparisons and fraction size comparisons. Turning to the dose comparisons, eight studies including three randomized trials reported freedom from biochemical failure and they reported increased freedom from biochemical failure with increased dose, and the strength of evidence for this outcome is moderate.

As you can see, these studies favored high dose external beam radiation therapy, and there was only one eligible study which looked at hormone therapy.

In terms of toxicity, there were nine studies, including a randomized trial, reporting no difference in genitourinary and gastrointestinal toxicity and the strength of evidence for this outcome is moderate. As you can see, there's no difference in acute or late toxicity.

And now going on to fraction size comparisons, three randomized trials reported

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freedom from biochemical failure and they reported no difference between standard and hypofractionation, and the strength of evidence for this outcome is moderate. As you can see, all three of them report no difference here.

In looking at genitourinary and gastrointestinal toxicities there are four studies, including two randomized trials reporting this outcome, and they found no difference in late or acute GU or GI toxicities. As you can see, there's no difference.

And the last comparison for this question is intra-low dose brachytherapy, and this has several studies comparing different isodose. In terms of overall survival, one retrospective study has reported increased survival with increased dose, and the same study has also looked at freedom from biochemical failure and has reported increased

freedom from biochemical failure with increased biologically effective dose. Another trial looking at iodine-125 has reported no difference in freedom from biochemical failure. The strength of evidence for this outcome is

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insufficient.

In terms of genitourinary and gastrointestinal toxicity there are two eligible randomized trials, and the first one comparing iodine and palladium showed no difference. And the second one looking at low dose brachytherapy without hyaluronic acid has found decreased gastrointestinal toxicity with hyaluronic acid, and the strength of evidence for this outcome is insufficient.

Now Dr. Ip will come back on the third question.

DR. GOODMAN: Thank you, Dr. Bannuru. Dr. Ip.

DR. IP: I'm going to just talk about the results on key question three, how do specific patient characteristics, example, age, race, ethnicity, presence or absence of comorbidities, affect the outcomes of these different forms of radiation therapy? In our search we actually did not identify any study that examined age, race or comorbidities in terms of how it affects the outcomes of radiation therapy.

All the studies that we found, they

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basically looked at how baseline risks would affect the outcomes, and basically here we have five studies that looked at whether, if you're classified as low baseline risk of disease progression of your prostate cancer into intermediate or high risk, and how the outcomes were changed. These classifications, as Dr. Dvorak mentioned, there's either an NCCN guideline or there's a D'Amico classification, they basically all use a variation of looking at the T stage and the Gleason score, or the PSA concentration, classify them into low, intermediate or high.

I'm not going to go over every single result. Suffice it to say that there is only one study per comparison, so we rated this as insufficient.

There is one randomized trial that examined how baseline PSA concentration would affect the outcome and they basically looked at 78 gray versus 70 gray, and found if you're in a group that PSA is less than ten, it didn't

seem to make any difference or affect the outcome, but if it's a PSA greater than ten then your failure seems to increase with

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increased external beam radiation therapy dose. One other study, a retrospective cohort study with about 4,000 patients, out of these 4,000 patients they identified the ones who had Gleason score of seven and they also identified the ones with Gleason score of eight to ten and compared them, and they found that with a Gleason score of seven there's no difference in biochemical freedom from failure with increased brachytherapy dose. However, in the group with a score of eight to ten, the biochemical freedom from failure is increased with increased brachytherapy dose.

This is just a summary slide of all the subjects you've heard. Basically we only found moderate strength of evidence when we're comparing intra-external beam radiation therapy dose in terms of biochemical failure and gastrointestinal and genitourinary toxicity.

Conclusions of our report: There are insufficient data to determine if radiation therapy is superior to no treatment or no initial treatment. We could not determine if one form of radiation therapy is superior to another form in terms of overall or

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disease-specific survival. Increased external beam radiation therapy dose associated with long-term biochemical control in brachytherapy is associated with increased genitourinary and decreased gastrointestinal toxicity compared with external beam radiation therapy.

Limitations: There's a paucity of high quality adequately randomized controlled trials. There's variability in many of the outcome measures. Even in definitions of biochemical failure, they seem to differ across the studies that we have examined. And lastly, the most important is in terms of the observational studies that we've looked at. Many of the comparison groups, their baseline risk of disease progressions are fundamentally different across the different trials.

For example, I notice in the brachytherapy studies they tend to enroll low risk patients and in the external beam therapy they tend to have intermediate or high risk patients. If you try to compare those two groups, it's problematic.

Future research: We recommend you

standardize the outcome measures. In terms of
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more trials we recommend comparing radiation therapy with no treatment or no initial treatment. In fact there are two ongoing trials, one is being done in the United Kingdom and one is done in Canada, we won't get the results from them for a few more years. We also recommend comparing the extreme hypofractionation versus standard fractionation, compare brachytherapy with external beam radiation therapy, and also look at the role of proton therapy versus photon therapy.
Lastly, none of the studies that we reviewed reported any kinds of data related to radiation therapy delivery in terms of safety, example, like errors in planning software or machine malfunctions, et cetera.
I would like to acknowledge Mei Chung, Joseph Lau, Ndidiamaka Obadan, Kamal Patel and Winifred Yu, who are not here today, but who worked pretty hard on this report. Thank you.
DR. GOODMAN: Thank you, Dr. Ip.
Before we finish this session, could you return to slide 101, please, and just leave that up for a moment. That was the chart. Now if you
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would just, if your team would just stay there for a few minutes, we're going to take a limited number of high level important, not detailed, questions from our panel before we move on to the next part.
Before we do that, though, we had one additional MedCAC member join us. Dr. Dmochowski, could you just introduce yourself and declare whether or not you have any conflicts.
DR. DMOCHOWSKI: Roger Dmochowski, Vanderbilt University. I'm a urologist and have no conflicts of interest.
DR. GOODMAN: Thank you, Dr. Dmochowski.
Doctor, we may have a couple questions now for you. Panel, we can't spend a lot of time on this, but just some high level questions to make sure we capture the essence of the presentation just given. Dr. Satya-Murti, did you have a question?
DR. SATYA-MURTI: Yeah, thank you. Thanks for the presentation. Very focused questions.
The definition of biochemical failure,
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is that a consensus or is that a validated definition, how much it rises? And the second is, a lot of these are insufficient evidence, and you referred to bias. What were the sources of bias, is that a design methodology?

DR. IP: I'm sorry, what bias are you talking about?

DR. SATYA-MURTI: In the studies you talked about bias and insufficiency. I mean it just stares at us, insufficiency.

DR. IP: Most of the time, this is very much an overgeneralization. There are very few studies in each of the studies, one or two, and a lot of these are observational studies so they're not randomized trials or anything, so that's why we rated them down.

DR. SATYA-MURTI: And biochemical?

DR. IP: Dr. Dvorak will answer that.

DR. DVORAK: That is a consensus definition.

DR. GOODMAN: Thank you. Dr. McNeil first.

DR. MCNEIL: I actually wanted an answer to Sandy's question.

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DR. GOODMAN: Okay. She's ceding the floor to Dr. Schwartz, and Dr. Schwartz, into the microphone, please.

DR. SCHWARTZ: I was just interested in the criteria that you used for deciding whether or not to do, you know, a summary meta-analysis when you had a bunch of studies that were small.

DR. IP: Well, first of all, we would prefer doing a meta-analysis of randomized controlled trials. Second of all, a lot of these observational studies are extremely heterogeneous and the comparator arms are very different, and to try to lump them together and give a summary estimate, it could be misleading. People would just say yeah, you know, overall they found this, and we don't want that to happen. So I think it's much safer to just report what each study shows, and you can decide for yourself.

DR. GOODMAN: Thank you. Dr. Fischer.

DR. FISCHER: Dr. Ip, if I understood you correctly, what you basically said in your summary was that there's no difference in treatment with external beam radiation, but

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that group was mostly low risk patients, in other words, what we're discussing today, T1

and T2 at the most. And then in the -- but the other group that was actually treated, that there was, these people were medium and high risk. Is my interpretation of what you basically said as a summary accurate?
DR. IP: I'm just saying that what I noticed in the studies, the patients who got the brachytherapy, they tended to be in the low risk group.
DR. FISCHER: Right.
DR. IP: The patients who got the external beam radiation therapy tend to be the intermediate or high risk group.
DR. FISCHER: So leaving in there, the patients who were in the low risk group, how old were they, that got the brachytherapy? Because there's a large, or at least there's some body of evidence that if they are older than 65, maybe they shouldn't be treated at all.
DR. IP: I don't know the answer to that off the top of my head. I'll take a look at that.

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DR. FISCHER: Thank you.
DR. GOODMAN: Thank you. Dr. Samson.
MR. SAMSON: I'd like to comment on the relation between your technology assessment and the Minnesota CER that was done in 2007. The study selection criteria used by the Minnesota EPC was focused on randomized trials, and your technology assessment was focused on not only randomized trials but observational designs. And I'm just curious if you think that there are other observational studies done before 2007 that you did not include in your analysis that maybe could be relevant.
DR. IP: That's an excellent question, and we actually took that into account. I don't have an exact answer because we didn't look at all these other studies. From what I could tell reading through the Minnesota report, they mentioned some of the observational studies and the difficulty. They also pinpointed the low quality of the observational studies, so they didn't even update it. So I suppose there could be some other observational studies, but I wouldn't know at this point.

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MR. SAMSON: Right, and one other comment. In your future research, you emphasize the need for randomized trials.
DR. IP: Yes.

MR. SAMSON: Would you also further that to say that you need some high quality observational designs?
DR. IP: Yes.
DR. GOODMAN: Thank you, Dr. Ip. Dr. Hevezi is next.
DR. HEVEZI: Dr. Ip, could you tell us how many of these studies were RTOG or SWOG sanctioned studies, or were they single institution studies?
DR. IP: I'm sorry, can you repeat the question?
DR. HEVEZI: Were these studies done under the guidance of the Radiation Therapy Oncology Group or the Southwest Oncology Group or any sort of cohorts like that?
DR. IP: I don't know the answer to that question.
DR. GOODMAN: You would have to go back to the original published report to determine it.

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Dr. Hevezi, why did you raise that question, sir, briefly?
DR. HEVEZI: Well, certainly the last point of Dr. Ip's summary was the safety aspect. One of the confounding factors here is that as the studies begin, there's a learning curve on how to proceed with them, and some of the studies would probably be less well done at the beginning of a study than maybe some of the patients treated at the end of the study, so those are some of the confounding kinds of factors that have to be taken into account. So if these studies were done under the guidance of RTOG or SWOG or some other oncology group, some of those factors could be leveled out.
DR. GOODMAN: Dr. McNeil.
DR. MCNEIL: I notice that in a couple of the studies the use of the androgen deprivation therapy had a large effect, there were large studies with a large effect. And I'm wondering if going forward you think it's reasonable or not reasonable to be looking at other studies that don't include these androgen deprivation therapies for this group of patients.

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DR. IP: I think that is perfectly reasonable.
DR. MCNEIL: Which is perfectly reasonable?
DR. IP: It should look at patients who only have T1 and T2 and did not receive any

form of hormonal therapy.
DR. MCNEIL: I guess what I was asking, is it possible in the studies in which that information is not provided, and I think there are only two slides here in which the presence or absence of androgen deprivation therapy is indicated, do we know for sure that in all of the other studies there was or was not any additional therapy?
DR. IP: We actually know that information; we just didn't summarize it in these slides.
DR. GOODMAN: Dr. McNeil, does that satisfy your question there?
DR. MCNEIL: Not completely. In terms of your future research, do we explicitly have to do studies that do or do not include androgen deprivation therapy, to tease these T1 and T2 tumors with the various kinds of

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radiation therapy?
DR. GOODMAN: Dr. Dvorak.
DR. DVORAK: If I could make one comment, on one of the slides there is the comparison of no androgen deprivation to androgen deprivation, and so it happens that the studies that were in the yes, androgen deprivation therapy, went back historically and had lower doses of external beam radiation therapy, so they were much more heterogeneous than the other three studies, so it may or may not be the androgen deprivation therapy effect.
DR. MCNEIL: So even though they're published recently, they were older?
DR. DVORAK: Correct. They went back to 1993 or 1994 in their retrospective cohort, and over that time the dose of external beam radiation therapy has changed dramatically as a function of the technology advancements. Having said that, your question I think is fair as to the role of androgen deprivation therapy, but we explicitly did not look at it as part of this report.
DR. GOODMAN: Thank you, Dr. Dvorak, and once again, Dr. Dvorak, please slow down by

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that 7.4 percent that I requested earlier. It's my failing, not yours, but I appreciate that. Dr. Potters.
DR. POTTERS: Yeah. On the next slide, 102, on the first bullet item, how comfortable are you with the no treatment or no initial treatment, versus no treatment and no initial treatment, since the comparison of

those studies included cohorts of patients that had delayed therapy which would then bias the no treatment?
DR. IP: I think you need to repeat the question, please?
DR. POTTERS: So, the first bullet item, you say there's insufficient data to determine if RT is superior to no treatment or no initial treatment. So, my definition of no initial treatment is important, because it's generally defined as a delay in treatment of six months or so, which may or may not be of significance given the fact that there is a large cohort of patients treated after six months in a lot of those observational studies, and how significant is the or versus and in that first statement?

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DR. IP: We took like a pretty comprehensive inclusion here, and basically we tried to come up with this term no treatment or no initial treatment because of all the varying definitions of active surveillance, watchful waiting and observation. So it isn't like an all-inclusive group, so we are now seeing you have to have treatment within six months or more than six. Some of these, Dr. Dvorak can explain better, some of these you could be watching and do nothing for years, and then you may get treatment if something happens.
DR. GOODMAN: Thank you, Dr. Ip. Dr. Potters, I would just point out, it sounds like a pretty inclusive, broad, encompassing definition, and even with that, there does not seem to be a lot of rigorous evidence.
DR. POTTERS: My only comment would be that if it's an and instead of or, because you don't have the evidence that defines no treatment versus delayed therapy.
DR. GOODMAN: I would prefer the Boolean logic or, which is more inclusive. I think we probably mean the same thing. Would you go back to slide 101, please, for a point

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of clarification? Top line, radiation therapy versus NT, does the RT there refer to all forms of external radiation as well as internal?
DR. IP: Yes, it's all forms.
DR. GOODMAN: It's all forms, including for example SBRT.
DR. IP: Right.
DR. GOODMAN: And I look across the first line, under disease-specific survival I see insufficient, freedom from biochemical

failure I see insufficient, GU/GI toxicity I see insufficient. So that is an all-inclusive line, is that correct?
DR. IP: Correct.
DR. GOODMAN: Thank you. With that, Dr. McNeil, a question?
DR. MCNEIL: Just to follow up on your question, if that is all inclusive, is there any relevance to answering the sub questions?
DR. GOODMAN: We will confront that issue shortly, but we do want to hear from our presenters. Dr. Satya-Murti.
DR. SATYA-MURTI: So going back to that first row, you don't have enough information on proton beam, I assume.

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DR. IP: Right.
DR. SATYA-MURTI: So we might say RT versus NT with, I suppose it's sufficient but not yet collected data on proton beam. Proton beam is not included, or is it included on the first row?
DR. GOODMAN: Dr. Dvorak.
DR. DVORAK: It was included in our external beam radiation therapy rule. However, none of the retrospective cohort studies that have looked at that comparison included proton there in that group, I believe.
DR. GOODMAN: Thank you very much. One short question, Dr. Jarvik.
DR. JARVIK: A very short question. This review went up to January 2010, is that right?
DR. IP: Right.
DR. JARVIK: Have you done any sort of informal review, say in the last month?
DR. IP: Yes. Dr. Dvorak is pretty much up to date, so a couple studies have published since then. We haven't done another -- we will do another update search in a month or so.

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DR. JARVIK: But the overall summary remains the same, essentially insufficient evidence?
DR. IP: Yes.
DR. GOODMAN: Thank you, Dr. Jarvik, thank you, Dr. Ip. Thank you very much to the Tufts EPC team, well presented, thank you very much. We know you won't be going anywhere anytime soon, and so therefore you will be available for further questions later on, and I'm sure there will be.
We are now going to proceed to our

scheduled speakers. And what we'll do is, we still plan on taking a break at about ten o'clock this morning, which means we won't get through all of our seven-minute presentations here. We will try to get through several at least before proceeding. And if the order I've been given hasn't changed, we're first going to hear from Dr. Peter Grimm, executive director of the Prostate Cancer Treatment Center in Seattle. Dr. Grimm, like all, you have your seven minutes starting now. Thank you.

DR. GRIMM: Thank you. It's an honor to be here. It's a pleasure to speak with all

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of you and my colleagues around the country. I would like to present to you some comparative effectiveness work that we've done with our colleagues around the country.

As you noted in the previous speakers' presentations, the information that we have for prostate cancer is insufficient to make conclusions, particularly about mortality, and largely we're stuck with retrospective studies to decide on the effectiveness of these treatments. To answer this question, 25, or 25 experts around the country, or around the world actually that you see here, gathered together to decide on a criteria and method to evaluate the world's literature, and this involved my colleagues from around the world, and as you can see, some of them are represented here.

The idea of this was to review all the world's literature from the year 2000, which is considered to be modern literature. We reviewed over 15,000 articles and abstracts, of which we found 603 that were treatment-related.

The articles were then screened by a very strict criteria as determined by the expert panel. This panel decided that the criteria

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for inclusion of an article into, to be evaluated for comparative effectiveness should include risk stratifications. As you know from the previous slides and speakers, there was no risk stratification bit there was allusion to the fact that we should stratify patients and we should look at them according to their risk groups because they do have different treatment modalities, they have different side effect profiles, and those are critically important.

A biochemical endpoint was established, a standard criteria, to answer some of the panel's questions. Clinical staging only, and there were no exclusions

allowed. As you know, most of you who have looked at prostatectomy studies, there's a lot of exclusions because of pathological staging and not preoperative staging.
The problem with randomized studies, as you noticed and that many of us know, is that radiation dose was inadequate to evaluate the current modality thinking on doses, and so 72 gray was selected as a minimum dose.
All of the modalities were considered, there was no modality not included in this

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study. Only peer-reviewed articles were reviewed. The studies had to have at least a minimum of 100 patients for the low and intermediate risk group, and a minimum of 50, and there had to be a median follow-up of five years.
The astonishing thing that is sort of a damnation of the literature and I think something we should all be aware of, is that there's very little criteria out there for article publication in terms of minimal criteria. The panel thought this was the minimal criteria that an article should have and only, less than 10 percent of the articles actually fit those criteria, and no robotic prostatectomy studies fit that criteria, and there's no stereotactic external beam radiation that fit it, no CyberKnife studies that fit that yet.
Most of them were stratification issues, but many of them also did not have five-year follow-up. We all know that if you look at data, either mortality or biochemical control rates, if you look at less than five years you're probably not looking at a study

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that's sufficiently, has sufficient time to separate the differences.
We did a very simple way of analyzing this with a scattergram approach to explain this that's very simple to understand. Each modality was given a symbol. As you can see, the blue dots here are brachytherapy alone, the surgeries are the red triangles, the green represent external beam. So these represent the studies, this yellow up here represents proton therapy. If you look at this group and look overall in terms of biochemical control rates, these are the biochemical control rates by PSA, progression-free analysis, and these are the years out.
So for example at 14, that's study

number 14, demonstrated 98 percent of the patients are free of disease ten years out, which we see the most in this low risk group. Overall, you can draw your own conclusions from this in terms of overall cancer control rates. If you're looking at treatment modalities, obviously treatment failure is expensive and represents greater modality to a patient, so you want to pick out a treatment that's most

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effective and is less likely to require a secondary treatment. But the good news here is this. The majority of low risk patients are going to do well no matter what you do, and that the challenge waiting for us is to decide which of these patient populations need brachytherapy as a modality because it, at least in this type of analysis, it appears to be somewhat better. Many of us had asked if a change in the criteria, a change in the follow-up time or the number of patients changed anything, and it really did not change anything, but in terms of analysis it gave us a lot more data points. So you can look at that and if you're interested, you can e-mail me and I will be happy to send this to you, and all these numbers inside these represent the studies that we looked at. We looked at the intermediate risk group for the same issue. These patients are a little more diverse group of patients. As you can see, some of them got external beam plus seeds, some of them got seeds alone, and this is the external beam and this is the HDR brachytherapy group.

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DR. GOODMAN: Two minutes.

DR. GRIMM: Okay, we're almost done. You can see here the brachytherapy group, either in single modality or combination therapy. To answer your question about hormonal therapy, it does not seem to have any advantage for the low and intermediate risk group when you use brachytherapy. If you look at the higher, if you get into the higher risk group -- and that is true for the intermediate risk group as well. When you get into the higher risk group, same issues are involved, hormonal therapy comes into play more for this group, but again, if you use a combination therapy they seem to do much better, with surgery only accomplishing maybe 20 to 50 percent, external beam radiation results are about 40 to 60 percent, and if you add hormonal

therapy, it does seem to help it a little bit. And whether you, if you change the criteria slightly, it does not change at all. So this is all the world's literature from 2000 to 2009. It will be updated here briefly. It has been presented at ASCO and ASTRO and is being prepared for publication

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now. So in conclusion, there's no randomized studies to date, as you noticed. The biochemical control criteria, by biochemical control criteria, brachytherapy alone or in combination appears superior in all groups. However, in low risk group, a majority of patients are going to do well no matter what treatment you do for them. The problem with most of the studies to date is they're not pre-risk stratified, and only a small number of these studies conform to some basic reporting criteria. I greatly appreciate the opportunity to present to this panel. Thank you very much.

DR. GOODMAN: Thank you very much, Dr. Grimm, well presented, thank you. Next is Dr. Howard Sandler, who is the Ronald H. Bloom chair in cancer therapeutics, professor and chair of the department of radiology oncology at Cedars-Sinai Medical Center. Welcome, Dr. Sandler.

DR. SANDLER: Thank you very much, Dr. Goodman, thank you, panel members. I have consulted for a couple of device companies

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within the past year, Variant and Calypso. Otherwise, no conflicts. For localized prostate cancer, there is no single treatment option that is clearly superior; in fact, there are multiple treatment options and it's hard to elucidate a definite advantage of one treatment over another, and there's no single treatment option that's appropriate for every patient. Frequently in consultation with a newly diagnosed prostate cancer, we'll go through the pros and cons of all of the localized treatment options with the patients. Just a few definitional things. External beam radiation therapy includes 3-D CRT, IMRT, image-guided radiation therapy, IGRT, and proton beam. IMRT is a specialized form of 3-D CRT that allows radiation to be more exactly shaped to fit the cancer. Brachytherapy, as we heard, treats the patients

with radioactive seeds.
I would like to dwell just a second on watchful waiting/active surveillance, and I think this addresses in part what Dr. Potters mentioned earlier. There is a substantial
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difference between these no treatment options. Where watchful waiting implies to practitioners in the field that absolutely no treatment is done until the patient becomes symptomatic, perhaps from metastatic or locally advanced disease, whereas active surveillance implies careful surveillance of the patient with frequent PSA testing, periodic biopsies, and intervention once a certain aggressiveness threshold is reached. As active surveillance is relatively new, it's still under conceptual development, there's no uniformity among practitioners of active surveillance on what qualifies as the disease progression to lead to intervention. There is no uniformity on what active surveillance means in terms of the frequency of PSA testing or the frequency of prosthetic biopsies to look for upgrading.
So to the questions, radiation therapy for the treatment of localized prostate cancer.
Survival of patients with localized prostate cancer who undergo radiation therapy and endocrine treatment is higher than those who receive endocrine treatment alone. This is a very important paper and I'll show a graph from
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this on the next slide.
Dose escalation as we've heard, with external beam treatment, leads to improvement in local and biochemical control, and there's several randomized trials, at least four that I'm aware of. Radiation therapy has a modest effect on urinary and sexual functional domains and a modest effect on bowel function, and I will demonstrate these.
So these are two graphs from the Widmark paper, a randomized study of hormones versus hormones and radiation, testing whether radiation therapy is beneficial. They showed a statistically significant improvement in overall survival with the addition of radiation therapy. Some of these patients were T3, but 20 percent of these patients were T1 and T2, and the effect size as shown in the forest plot in this paper show that there's the same beneficial survival effect for the T1 and T2 patients with the addition of radiation therapy. My dashed line there just indicates

that most of the deaths of these patients were from prostate cancer. These were not a group of patients who were likely to die from other

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things, these were serious prostate cancer patients who benefitted from radiation. These show an improvement in biochemical control from higher doses of radiation therapy from two of the four randomized trials. The effect size is very consistent.

And this is an important paper, maybe I'm a little biased because I'm a coauthor, but Marty Sanda presented this data in the New England Journal in 2008 in a contemporary series of surgery and radiation patients showing significant short-term quality of life diminution with radical prostatectomy and relatively modest effects from radiation therapy. In the middle curves the dagger there shows a clinically insignificant difference compared to baseline for radiation therapy as far as sexual score.

DR. GOODMAN: About two minutes, Dr. Sandler.

DR. SANDLER: Question two, radiation therapy compared to active surveillance. There's an ongoing clinical trial showing that it's not well established that active

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surveillance is a standard of care. I'm a member of the DOD prostate cancer research integration panel. This year we are asking people to submit grants as part of a new grant program to see if we can identify what cancers are lethal and need treatment. The reason I point this out is it just indicates, I think, that the overall understanding of which cancers need immediate treatment and not is a research question, and not ready for prime time.

I think in order to make my seven minutes I'm going to skip ahead a little bit. There was a question about Medicare and community-based settings. Clearly prostate cancer is a Medicare-patient-aged issue and radiation therapy, especially with IMRT, has made it into the community. The RTOG, a group that I'm a part of, indicates that IMRT can be used in community settings.

I think I'm just going to go to my conclusion. In conclusion, radiotherapy is an important and clinically proven therapeutic tool in the fight against prostate cancer.

It's been proven to reduce mortality as shown
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in the Widmark study, and provides excellent functional outcomes as shown by the Sanda experience. There is no single therapeutic treatment that's been shown to be appropriate for all patients. Thank you.
DR. GOODMAN: Thank you very much, Dr. Sandler. Thank you in particular for the distinction early on between watchful waiting and active surveillance.
Our next speaker is Dr. Luther Brady, who is the distinguished university professor, Hylda Cohn/American Cancer Society, a professor of clinical oncology and professor in the department of radiation oncology at the Drexel University College of Medicine. Welcome, Dr. Brady.
DR. BRADY: Thank you very much. I have no conflicts of interest.
One of the points I think I would like to make is that this issue about what is important relative to the management of patients with cancer of the prostate is not a new issue. In my own personal experience, it began probably in the early 1960s with reports by Malcolm Bagshaw from Stanford, and also too
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by the Erskine lectureship given by Juan del Regato at the Radiological Society of North America, indicating that radiation was indeed an appropriate proper treatment for patients with cancer of the prostate.
I think that the questions need to be revised in some sense and I will deal with those as we go through the various questions.
I am very confident that the question number one is an important question and needs to be addressed in a controlled fashion to identify what represents the best treatment program for patients with localized prostate cancer.
In question number two, I am confident that the evidence at the moment is enough to conclude that external beam radiation therapy does improve the health outcome for the patients compared to watchful waiting. Some of that evidence has already been brought to the attention of the panel this morning. The category of external beam radiation therapy is broad and it needs to be uniquely discussed with regard to the different treatment methods that are available. And that of course
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includes not only image guided radiation therapy but stereotactic body radiation therapy and also proton beam therapy, as well as image-guided radiation therapy. Particle therapy or proton beam therapy ought not to be mingled in my opinion among the other mechanisms for radiation therapy. So therefore, I think that it's important for the panel to consider the development of programs that would look at each of these issues without mingling them all together in one basket.

The third question about how confident I am relative to the evidence, I think that brachytherapy has been established to be good in terms of management for low grade, or let's say low risk patients with cancer of the prostate, and we have published in the 1980s ten-year follow-ups on patients that were treated in the Memorial Sloan-Kettering group, looking at external beam radiation therapy and brachytherapy using I-125 seeds as the implantation, showing that the brachytherapy was equal to appropriately devised external beam radiation programs for T1 lesions of the prostate but not so for T2 and T3 lesions. So

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therefore, I think that one needs to look at that issue.

And also the issue of interstitial utilization of iridium or high dose rate brachytherapy procedures, that should be dealt with as another question.

In question number four, how confident am I that the evidence is adequate to conclude that each of these treatment modalities does improve the health outcome? And obviously listed for you on this slide are all the various issues and also too, the issues that have been brought up by other presenters relative to mortality, functional outcome and adverse events. So I think that in question number four the, all external beam radiation therapy, IMRT, and perhaps IGRT and stereotactic body radiation delivery devices including CyberKnife, have been cleared by the FDA as appropriately approved instruments for utilization in radiation therapy.

I do have some significant concerns about why a single modality like stereotactic body radiotherapy is excluded, or is being held to comparison to other standard treatment

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programs. SBRT should be compared to watchful waiting consistent with the standards

established in questions two and three. To my knowledge, there have been no head-to-head trials comparing any of the treatment modalities under consideration and I think it's difficult for MedCAC to answer the question four as posed, since there really is no relatively good data available at the moment, as has been pointed out already.

In conclusion, the appropriate comparator to photon beam therapy for prostate cancer is watchful waiting, as all of us I think in this room recognize. All forms of photon beam radiation therapy should be compared separately to watchful waiting because there are no head-to-head trials comparing different radiation treatment modalities that have been published. And proton beam therapy should be considered separately from photon beam therapy on the basis of the evidence that's available at this particular point in time. I thank you very much.

DR. GOODMAN: Thank you very much, Dr. Brady, we appreciate your comments. Next is

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Dr. Albert Blumberg representing the American College of Radiology. Dr. Blumberg.

DR. BLUMBERG: Good morning. On behalf of the college, we appreciate the opportunity to be able to present to MedCAC this morning. I'm Albert Blumberg and I am the current chair of the Commission on Radiology and Oncology for the American College of Radiology.

You're going to hear a lot today about the research, and I'm not going to reiterate the comments that have already been made about the strength of the research. It's clear that more research is needed, and the college has lots of activities in these areas. My comments I'm sure have been circulated to the panel.

We specifically are involved in three areas. We have an active guidelines and standards program where we evaluate the practice of radiation oncology through a consensus development situation and achieve collaboratively with ASTRO and other radiation oncology societies a sense of how the community should proceed in this area. We have a Delphi derived process which is our appropriateness

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criteria.

We rate all of these various standards and to date all of the types of treatment you're talking about except for stereotactic

body therapy where the technique is new and the data is young, have been evaluated. In our current redo of our appropriateness criteria we are looking at active surveillance and are going to include that in the next issue, which should come out in the current calendar year. And as has already been mentioned by several speakers, the RTOG has been actively involved in prostate cancer studies for years, and for those of you who aren't aware, the RTOG has always been a part of our college since its inception over 40 years ago and is an integral part and foundation, frankly, of our research efforts in radiology.

The problems that are existent primarily come from, in my opinion, the fact that we really don't have a wealth of studies to meet certain evidence criteria as pointed out by the technology assessment already presented, and clearly there needs to be more research in this area. One of the ways the

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government could help would be to provide more funding for cooperative groups such as RTOG who wish to move the envelope further in this area. Part of the problem where I know there's active interest, in looking at can we identify a cohort of men for whom active surveillance would be a preferred option as opposed to just an option, and part of the problem, and I think everyone who deals with patients on a clinical basis would agree, that it's very difficult sometimes to explain to a patient that active surveillance is an option that they should consider when all they hear is that they have cancer. And they're very concerned, upset and mesmerized by that diagnosis, understandably so, and they may actively choose not to pursue active surveillance. And it's very hard sometimes in a randomized control fashion to convince people to take one of various, what we consider as physicians and researchers treatment options, and clearly the active surveillance option is one that is many times a difficult one to sell. And I think until we crack that nut, it's going to be difficult to perhaps accumulate the data

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in a randomized controlled fashion to achieve the kind of data that I think all of us would like to have to know how best to advise patients. And also, I think we need to have more basic biochemical marker studies to see if

there are types of prostate cancer that meet certain histochemical or histopathologic criteria that would allow us to say you have this finding on your biopsy and therefore you fit into the group where active surveillance could legitimately be perhaps your number one choice when you take into account your age and other comorbidities.

With that, I thank you for the opportunity to present some comments to you today.

DR. GOODMAN: Thank you for those comments, Dr. Blumberg. Next is Dr. Sean Collins, with the department of radiation medicine, Georgetown University Hospital, and Lombardi Comprehensive Cancer Center. Welcome, Dr. Collins.

DR. COLLINS: Thank you for giving me the opportunity to speak today. The title of

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my talk is Stereotactic Body Radiotherapy for the Treatment of Localized Prostate Cancer. I'm in the department of medicine. I'm also a member of Lombardi Comprehensive Cancer Center. I'm board certified, I'm the director of the prostate CyberKnife program at Georgetown. I've treated over a thousand patients with stereotactic body therapy and I've treated over 250 patients with prostate cancer. I have no conflicts of interest. The reason I'm here is I want to maintain access to the CyberKnife for my patients who want it.

Since September 2008, the ASTRO emerging technology committee report on stereotactic body radiotherapy for prostate cancer, several studies totaling over 600 patients have been published. And King from Stanford University has published his data in the Red Journal. Also, Friedland and Freeman from Naples have published their data. Byers, from the Swedish Cancer Center in Seattle, has published his data. And Dr. Katz, who will talk more today about the patients that he's treated with stereotactic body radiotherapy. Over the past several years with the

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accumulation of this data, four out of four Medicare contractors, Highmark, Wisconsin Physician Services, First Coastal Services and Palmetto, have finalized appropriate prostate cancer coverage with LCDs, and this reflects the data that's emerging and also the standards in the community practice.

This table basically shows how

stereotactic body radiotherapy mimics the dose intensity and specificity of high dose rate brachytherapy. Both treatments can deliver high peripheral doses to regions of highest cancer cell density. Both treatments can be completed rapidly in five to ten days. Both give total doses of about 35 to 40 gray. Both have steep dose gradients that limit radiation exposure to critical surrounding structures. Importantly, stereotactic body radiotherapy is not invasive, does not require anesthesia, and allows more of the Medicare population to actually undergo this treatment. Also, if you look at the differences and similarities between all the standard radiation options, I consider the standard radiation options stereotactic body

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radiotherapy, HDR brachytherapy, low dose rate brachytherapy, intensity modulated radiation therapy, 3-D conformal radiation therapy and proton therapy as the standard treatment modalities.

Stereotactic body radiotherapy is very similar to HDR and LDR because it allows continual image guidance throughout the treatment. Your prostate actually moves in six different directions and you can actually miss it if you're not paying attention to where it is, so I think continual image guidance is very important in the treatment of prostate cancer. And not only continual image guidance, you have to have the ability to actually adjust your beam accordingly with motion, so you both have to have the ability to adjust for motion and to know where the prostate is.

Like IMRT, 3-D conformal and proton, stereotactic body radiotherapy is not invasive. It's a short treatment time, five to ten days, so it's convenient for patients who -- there are many 60-year-olds who still have busy lives, who are active, who want to maintain those busy lives, and it's very convenient. It

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does not require anesthesia, does not require an operative procedure, which once again makes it a good treatment option for elderly patients who have, who cannot get HDR or LDR because of those.

If you compare the outcomes between the different standard radiation techniques you see that they all have low rates of late toxicity. Late grade three urinary toxicity, I apologize, this is a typo, late grade three

toxicity is zero to five percent for stereotactic body radiotherapy, and it's also similar for the other standard radiation treatment options. Late grade three rectal toxicity is also very rare in all the treatment options, approximately one percent. All the treatment options are very good at preserving sexual function, about 40 to 80 percent, and they all provide excellent biochemical disease-free survivals and are all excellent treatment options for prostate cancer. Once again, I just want to emphasize that they're all good at preserving sexual function, which we know is important to American men.

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If you look at SRT, it's less expensive than most other forms of radiation therapy. If you look at the 2010 Medicare reimbursement for major radiation therapy options, this is stereotactic body radiotherapy. Other treatment options like IMRT and proton beams are much more expensive than stereotactic body radiotherapy. If this number looks a little bit low to you, it only includes treatment planning and treatment delivery. I did not include the costs of the physicians.

In conclusion, these are my summaries from my talk. Stereotactic body radiotherapy can achieve radiation doses similar to HDR brachytherapy noninvasively without anesthesia and without operative risk. The published data suggests that the toxicity and the efficacy is similar to other types of radiation therapy. The ASTRO ETC predates the majority of the stereotactic prostate cancer literature that is now available, so many patients have been reviewed and are now in the published literature to see what the outcomes with stereotactic body radiation therapy are. This

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ASTRO ETC stopped looking at trials in 2008 and most of these studies came out after 2008. Four out of four Medicare contractors have finalized appropriate prostate cancer coverage in their LCDs. The February 2008 AHRQ report, comparative effectiveness of therapies for clinically localized prostate cancer, concluded that there is no one single therapy that can be considered the preferred treatment for localized prostate cancer. No subsequent data that I have heard today from the excellent

talks suggests otherwise. Due to the lack of randomized trials showing superiority of one treatment over another, current data supports stereotactic body radiotherapy as a treatment that should be available to the Medicare population, and for my patients I hope you allow it to continue to cover for stereotactic body radiotherapy. Thank you for letting me speak today.

DR. GOODMAN: Thank you very much, Dr. Collins, for your comments.

What we'll do now is, I think we'll take our ten o'clock break now, and if you just

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take a look at your watch or the information technology in the palm of your hand and add 15 minutes to that, we will reconvene headed by Dr. Carl Olsson. See you in 15 minutes. Thank you.

(Recess.)

DR. GOODMAN: Let's find our seats, please, and we will reconvene. And our next speaker, panel, our next speaker is Dr. Carl Olsson. He's the John K. Latimer professor and chairman emeritus -- panel -- chairman emeritus of the department of urology at the College of Physicians and Surgeons of Columbia University, and he's here representing the American Urological Association. Welcome, Dr. Olsson.

DR. OLSSON: Thank you. Good morning all. My name is Carl Olsson, and I'm pleased to give commentary on behalf of the AUA. I am past secretary of AUA and also CMO of Integrated Medical Professionals. The AUA represents over 90 percent of the practicing urologists in the United States and over 50 percent of its patients are actually Medicare beneficiaries. AUA members are clearly major stakeholders in any discussion of prostate

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cancer because we're the docs who make the diagnosis and we are the ones who initially guide our patients to different forms of therapy.

Selecting the right choice of management is really a complex thing for the individual patients. We have to have his age, state of health, life expectancy, tolerance for risk, tolerance for risk of potential adverse outcomes, and we have to also consider his tumor, his Gleason scores, his PSA value, tumor grade and tumor volume, and tumor stage. Finally, the advising doctor has a role in this matter as well.

A recent review of 85,000 Medicare beneficiaries on this very issue showed that if a patient saw only a urologist, he would choose surgery as his treatment. However, if he saw a urologist and a radiation oncologist, almost 80 percent of patients would choose radiation, so that shows how convincing we are. Overall, of 85,000 patients, elected radiation therapy was 42 percent, surgery in 21 percent, and expectant management in 20 percent. So we are holding there with regard to getting people on

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board to some watchful waiting or active surveillance.

Before answering the first question, it's important to know if any treatment at all is good for prostate cancer compared to nothing, and that's been reviewed and answered by the Scandinavian group which showed the incidence of death over eight years from prostate cancer, distant metastases, and local progression were all statistically reduced in the surgery group. There aren't any really good studies of radiation versus no treatment, so we used a surrogate looking at dose escalation studies and interestingly, in every study that we looked at, we found an interesting thing. Whether it was for 3-D conformal, IMRT, brachytherapy or even proton beam, dose escalation was always favoring a drop in mortality or prolongation of the bNED interval.

I can't comment on the significant risk of adverse events with all these different treatment modalities. As you heard this morning, comparators are dreary at best. I can say that some forms of radiation affect, all

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forms of radiation affect bowel and sexual function to some extent. To some extent brachytherapy is perhaps the worst because it involves a good deal of urinary and bowel as well.

Before answering the second and third questions, I think we should know something about the prevalence of surveillance in the United States and overseas. Recent CAPSURE data on 12,000 men showed that less than seven percent of men chose active surveillance. In the Medicare study I mentioned earlier, as you can see, 20 percent chose expectant management, so at least in the older population we're making progress.

We should also appreciate what the

problems are with active surveillance. All surveillance series are small, they have short follow-ups, there are no standard criteria for choosing candidates, there's no standard protocol to follow, there's no standard agreement on what triggers failure of surveillance, and most importantly, there's always the possibility of missing the window of opportunity for cure.

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DR. GOODMAN: Dr. Olsson, about two minutes, sir.

DR. OLSSON: All right. Our answers to questions six and seven can be combined because they are about the same. The most often cited quote related to prostate cancer care is one attributed to Willet Whitmore, who was former chief of urology at Memorial Sloan-Kettering before he succumbed to this very disease. What Whit said was, is cure possible, is cure necessary, is cure possible only when it isn't necessary? These questions are very similar to what we're facing today in the way of questions from MedCAC. The only difference is that Dr. Whitmore started this quotation 40 years ago.

So, we all know that some of the patients that we see have to be cured, because we have patients that are still dying from the disease. But how do we identify these cancers from the ones where a cure may not be necessary? In my written thing I present two recent studies, one on trichomonas vaginalis seropositivity that predicted for high grade prostate cancer and prostate cancer death, and

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another on gene rearrangements where 11-year survival could be predicted from the time of diagnosis comparative to patients who don't have these rearrangements.

So in summary, I think that efforts should be made to study these issues more vigorously than they have been studied, and with that we can find out perhaps which patients can have treatment delayed or cancelled altogether. I thank you for your time.

DR. GOODMAN: Thank you very much, Dr. Olsson, for your perspectives. Your points are very well taken, sir. Thank you. Next is Andrew Lee, who is an associate professor for radiation oncology at M.D. Anderson Cancer Center. Welcome, Dr. Lee.

DR. LEE: Thank you very much. I just

want to take this opportunity, by way of introduction, I did my residency at the Joint Center for Radiation Therapy in the Longwood Medical Area, I got my M.P.H. at Harvard School of Public Health, and I have been at. M.D. Anderson treating prostate cancer primarily for the past nine years. I have no relevant

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disclosures.

A few key points I want to make. I think the distinction between what watchful waiting really is between observation and active surveillance, we understand that those two things are not synonymous. In reality, Gleason scores of two to five probably are no longer being diagnosed. Untreated prostate cancer does have a tendency to progress. More advanced prostate cancer does require more therapy. Higher doses of radiation therapy do provide a clinical benefit, and specialized techniques are routinely needed to deliver this dose safely with low morbidity.

This is the crux of the matter. If you look at the red line, that's the death from heart disease. That is the number one competing cause of death for men of prostate cancer age and that line is going down. So independent of overall survival, we do need to look at any number of other important metrics and some of these are listed here.

And I don't want to deemphasize hormone-free survival. We all know that hormone therapy has significant toxicity

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associated with it. This is a patient with widely metastatic prostate cancer. I will tell you up front that this patient has a number of comorbidities, may not die from this disease, but I'll tell you that this patient is miserable.

Dr. Sandler alluded to this slide already, and I thought he did a nice job. I just want to make the point about active surveillance, that it does require monitoring. And I'll tell you that repeat biopsies are not without their own set of side effects. Actually the sepsis rate for biopsies is going up because of multidrug-resistant bacteria, and I have had patients followed on active surveillance protocols that some go off because they don't want to get another biopsy. We also have to keep in mind that some of the patients as they get older, they may develop other comorbid conditions that may not be fatal, but

may make it difficult for them to receive definitive therapy for their prostate cancer. When we look at the population observation studies, the mortality was low for Gleason scores that were two to six or two to

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five, and that's probably true. For example, Gleason scores of two are probably now called adenosis. So they were right, it wasn't even really prostate cancer. Keep in mind that in these studies, upwards of 60 to 80 percent of the men were actually receiving hormone therapy at some point in their lives, and I guarantee you they were receiving it lifelong. We also have to keep in mind that chemical castration for these men is not considered conservative therapy, so when we talk about T1 and T2 prostate cancer, we don't want to lump everything together. There is a spectrum of disease and how aggressive it can be, and in general the lowest risk patients probably could be addressed with monotherapy, a single therapy. But as they progress into intermediate and even high risk patients, they probably need additional therapy in order to get the same cure fraction. Not only is this potentially more toxic, but it does cost more money. I just want to reemphasize this point about hormone therapy. There's a number of side effects that have been reported in the

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literature and it is somewhat dependent on how long you're receiving this hormone therapy. And I will tell you that having given hormone therapy to men with high risk features, that testosterone recovery after long-term hormone therapy is certainly variable. Dr. Sandler already alluded to this study by Dr. Widmark from Scandinavia, and I just want to draw your attention to the overall mortality. If you look at the risk reduction of .68, that's actually double the risk reduction that's used to justify cytotoxic chemotherapy in early stage breast cancer. So giving radiation therapy to these men, that did include T1 and T3s. Two studies have also been alluded to regarding two dose escalation randomized studies with external beam radiation in the U.S. One was done at Indiana with some x-rays, one was done in combination with Mass General and Loma Linda. The second one used a combination of x-ray therapy with proton

therapy. Keep in mind that not only was there a PSA control benefit, but the number of patients who needed salvage hormone therapy was
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less when they received higher radiation doses. And if you look at the, this has subsequently been updated, but the PSA control rates in this study were quite high, upwards of 90 percent. And so if you just look at the low risk patients, and this was done in a prospective fashion, their freedom from failure was close to 94 percent, and this data has been upheld with nearly nine years of follow-up. It's just graphically represented here for all patients and then just for those patients with low risk features.
Now in terms of the side effects from randomized trials in dose escalation, the first two at the top, M.D. Anderson's trial used x-rays, the bottom one used proton therapy, and the one from the University of Florida is just a single institution report. The grade three side effects are really what are life changing for the patients, those are the majority of the side effects that the panel was asking about in terms of side effects that may not be reversible. The grade two stuff, most of the time that can be managed, often as an outpatient. So if you look at the grade three
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and higher GI and GU side effect rates when you use x-rays, it gets you a little bit higher than any of the proton-based series.
DR. GOODMAN: Less than two minutes, Dr. Lee.
DR. LEE: In terms of the side effects with modern local therapy, every definitive local therapy is going to have some measure of side effects associated with it. And in general for incontinence, surgery is probably worse than any radiation. For bowel symptoms, radiation is probably a little worse than radical prostatectomy. And for sexual dysfunction, dependent upon whether or not a bilateral nerve sparing procedure is performed, everything is not great. Keep in mind that in any of these studies, the radiation patients are typically on average ten years older than any of the surgical-based series.
If you look at urinary incontinence, this is just one study, and look at the function compared to the baseline function, for radiation at the top, radical prostatectomy at the bottom. You can see that those curves

really don't change pre versus post function,
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and that's also the case with bowel symptoms.
We also have to keep in mind, as
Dr. Sandler pointed out, that there's not one
treatment that's good for every single patient.
We do a lot of brachytherapy at M.D. Anderson
but this is an example of a patient that may
not be a good brachytherapy candidate. It's a
65-year-old, the prostate volume is a little
bit large, and their AUA symptom index is not
optimal.
DR. GOODMAN: You may want to move to
your summary slide, Dr. Lee.
DR. LEE: Yes, sir. And this is just
a sagittal MRI showing that effect, that
hypertrophic median lobe for the post implant
morbidity for this patient is probably going to
be pretty high.
So in summary, there is evidence for
the efficacy of radiation therapy in this
disease. There's level one evidence showing
increased benefits with increase in that
radiation dose, and that advanced technologies
can accomplish this dose escalation without
significantly increasing toxicity.
Furthermore, we understand that patient
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selection is important. External beam
radiation therapy is still a very flexible
therapy for wide ranges of diseases as well as
for patients. We're not saying that these
other therapies are not good, but they may have
more limited applications for select patients.
Thank you.
DR. GOODMAN: Thank you very much,
Dr. Lee. And Dr. Lee, as is so for the other
speakers, we hope that you will remain here for
the balance of the day in case any questions
arise. Next is Dr. Gregory Merrick, from the
Schiffler Cancer Center and Wheeling Jesuit
University in Wheeling, West Virginia.
Dr. Merrick, welcome, sir.
DR. MERRICK: Hello. Thank you for
having me. What I'd like to do this morning is
real quickly talk a little bit about
brachytherapy and some comparisons to other
approaches.
The advantages of brachytherapy versus
prostatectomy is that we have a much more
generous periprostatic margin so we're much
more likely to encompass areas of extracapsular
extension, which is important especially in
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intermediate risk patients that have a very wide propensity for extracapsular disease, but a low chance of pelvic lymph node involvement. And when compared to external beam with dose escalation, if dose escalation is important, brachytherapy wins, we can give substantially higher doses.

The shortcomings of brachytherapy is the inability to treat pelvic lymph nodes, but unlike some of our other competing local modalities such as cryosurgery and CyberKnife, we have been able to demonstrate safely that pelvic lymph nodes can be attacked with the use of supplemental external beam.

Our long-term results, this is from our institution of over 1,600 patients at 12 years, median follow-up of 7.2 years. We have always used the Mayo Clinic definition for biochemical control, their surgical definition, a PSA less than 0.40. So we use a cut point in our Wheeling-Seattle studies. And what we've shown is that the cause-specific survival is about 98 percent, and the biochemical control rate is 95.

And unfortunately this morning, there

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were some allusions that brachytherapy is primarily for low risk men. That is not true. In this series 27 percent of these men were intermediate risk and 28 percent, 473 had high risk disease. And part of the reason we're so effective is these extracapsular margins. Brian Davis at the Mayo Clinic had shown that when there is extracapsular extension, 99 percent of the time it's less that five-millimeter margins, and looking at a sagittal reconstruction of an actual palladium model therapeutic implant, the margins are more than six millimeters at the 100 percent isodose line everywhere except posteriorly, and whenever evaluating brachytherapy, dosimetry is essential in order to determine the outcome.

When we looked at low risk, and in a lot of these gentlemen of course, we need to reassess as to who does need to be treated, but 40 percent of low risk men still receive androgen deprivation therapy. These are our results at 12 years in men who did not receive any supplemental beam or androgen deprivation therapy, and 0.44 percent died with an ablative PSA of less than 0.03.

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We've also shown the same thing for intermediate risk, and the standard of care is

the addition of supplemental beam. We currently are completing a prospective randomized trial that will hopefully further substantiate using monotherapy in intermediate risk patients where once again, our biochemical control rates were 96 percent, and on this selected group of intermediate risk patients, no one died.

But I think the most important thing is how do we deal with high risk, with high Gleason score, with double-digit PSAs. And in our series only a little bit less than six percent of men were dead of prostate cancer at 12 years. So I think the brachytherapy, and most of these men did have supplemental beam and about two-thirds had androgen deprivation therapy short course. I don't know of any other modality that shows such favorable results for higher risk disease.

So how does brachytherapy compare against prostatectomy, or how does radiation compare against prostatectomy, and that's important, because one of the questions here is

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treatment versus no treatment. We have a prospective randomized trial that demonstrated that prostatectomy improves survival in comparison to watchful waiting. With low Gleason scores, I think we'd do well regardless of treatment, but this is a combination slide of outcomes for Gleason eight to ten, and the reds are all the brachytherapy data from Richard Stock's group, from Atlanta, Seattle, the Wheeling series, and you can see that the prostatectomy series for eight to ten all cluster substantially below.

When we looked at prostate cancer death rates, there was recently a very large radical prostatectomy series published from Memorial, the Cleveland Clinic and Michigan, with about 12,000 patients. The median follow-up was only four years. Looking at our series of our over 1,650 patients when we looked at prostate cancer death rates, they reported ten and 15 years, we report 12 years. Whether it's low, intermediate or high, brachytherapy compares favorably, and especially with high Gleason scores of eight to ten. 16 percent of patients undergoing

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prostatectomy were dead at ten years, 34 percent at 15 years, our results were seven percent. This paper is currently in press.

DR. GOODMAN: Dr. Merrick, I notice

you have quite a few slides left but only two minutes, so I hope you will zero in on your main points.

DR. MERRICK: I'll just get through with this. Brachytherapy-related morbidity, there is a paper published this month from the Journal of Urology, Shellhammer's group, which demonstrated that brachytherapy had better urinary and better sexual function compared to either robotic, open prostatectomy or cryosurgery. However, radiation therapy was not part of that, and as such, I will jump over the rest of these slides relatively quickly. Cause of death, even at high risk, with prostatectomy, we see that prostate cancer death is greater than diseases of the heart, but as treatments become more effective, other competing modalities become more prominent. In our series, diseases of the heart were twice as likely to cause a high-risk man to die than prostate cancer, and I think it's one of the

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things we really need to start to do as urologic cancer physicians is to spend more time on cardiovascular health and wellness. I do disagree with stereotactic, some of the results shown. There's less than a hundred patients in manuscript form, there has never been a high risk patient reported in either the Virginia, Mason or Stanford series, 69 were low risk, 12 were intermediate risk. There are high risk patients presented in abstract form. There is no long-term follow-up. Treatment costs have already been shown.

And in summary, brachytherapy, I think the biochemical outcomes are favorable and durable for all risk groups. Prostate cancer death rates are extremely low. Morbidity compares favorably with competing local modalities through all series that have evaluated it, and it's the least expensive definitive treatment modality. Thank you for your time and attention.

DR. GOODMAN: Thank you very much, Dr. Merrick, we appreciate your detailed input. Thank you, sir. Next is Chrissie Kotwica,

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R.N., B.S.N., CyberKnife Coalition member, and from CyberKnife Centers of Miami and Palm Beach. Welcome, Ms. Kotwica.

MS. KOTWICA: Thank you very much. Thank you for allowing me the opportunity to talk to the committee this morning. My name is

Chrissie Kotwica and I'm representing the CyberKnife Coalition. My past professional experience is as manager and as patient navigator for the CyberKnife Center in Central Florida Regional Hospital. Currently I am the physician liaison and data manager for the CyberKnife Centers of Miami and Palm Beach. Personally I am a survivor.

A little bit about the coalition. It was formed in 2003 and incorporated in 2005. The coalition is a nonprofit association of CyberKnife user institutions. Our goal is to try to promote the patient's access to the lifesaving technology by working to insure accurate and adequate reimbursement through education, payer and governmental advocacy. With a large body of academic support, the CyberKnife has now treated more than 80,000 patients worldwide and has been installed as

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the radiosurgery system of choice by more than 190 institutions globally and 117 in the United States and Puerto Rico, many of whom are members of our coalition. The coalition did put out a survey recently that developed an online ability for our patients and our members to better understand how treatment decisions are made, and to provide a mechanism for patients to share their CyberKnife treatment experiences. 235 survey respondents responded as of March 22nd, 2010; that number has continued to grow. 71 of these respondents were CyberKnife patients. The remaining respondents are family and/or concerned citizens.

As you can note here on this bar graph, the clinicians presented their patients with many options for treatment of their localized prostate cancer, and here is how they answered. CyberKnife and prostatectomy ranked among the highest, with IMRT and watchful waiting to follow. These are all results by patients only on this slide.

Notice that some patients who chose CyberKnife did not receive information from

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their clinician but obtained information from a variety of outside sources such as family, research and Internet services, then made their decision based on those outside sources.

Reasons for choosing CyberKnife, patients chose CyberKnife over the treatment options because of the following factors: They were most comfortable with the side effects.

They seemed to like the best options among their choices, it offered the latest technology. It was convenient. Most likely to eradicate and eliminate the cancer. Least amount of time away from work. And they weren't a surgical candidate.

99 percent of patients described their treatment as successful. 58 percent of patients did not experience any side effects. 42 percent of patients did experience some side effects, including mild fatigue, mild burning during urination or loose bowels; the majority of the patients who experienced side effects indicated symptoms resolved within one to two months post treatment. 11 percent of the patients indicated they had some complication from treatment, including erectile dysfunction,

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urinary complications, bowel complications; however, a majority of the patients who experienced complications indicated resolution.

Patients request continued coverage for CyberKnife. 77 percent of the survey respondents indicated their CyberKnife treatment was covered by insurance. 12 percent of these patients indicated their treatment was not covered, and they had to appeal the insurance decision. Six percent of the patients indicated their treatment was not covered and they paid for their treatment out of pocket.

Patients, their families and other concerned citizens indicated that CyberKnife should continue to be covered by insurance and/or Medicare because of successful treatment options for localized prostate cancer. They also answered that patients should be offered all treatment options available today.

Convenient treatments that fit into the patients' lifestyle and because patients should not be denied treatment when they need it most.

Overall satisfaction was very high.

93 percent of our patients indicated that

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CyberKnife did not interrupt their normal life routine. 98 percent of patients indicated they would recommend CyberKnife treatment to others, and 99 percent of patients indicated they would choose to be treated with CyberKnife again.

Thank you for allowing me to speak to the committee today.

DR. GOODMAN: Thank you very much, Ms. Kotwica. As always, we hope that you will stay around for questions, and we always appreciate

input from patients directly. That's very important to our deliberations, thank you very much. And I might add, we also appreciate it when the quality of the evidence for patient data also rates high when we think about the quality of that evidence.

Next is Dr. Alan Katz, who is the associate professor of radiation oncology and medical director, department of radiation oncology, University of Rochester Medical Center. Welcome, Dr. Katz.

DR. KATZ: I am Dr. Alan Katz but I'd just like to clarify the record, I'm not at the University of Rochester, it's a different Katz. I'm at Winthrop Hospital outside of New York

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City.

DR. GOODMAN: Thank you for that clarification. I'm sure the other Dr. Katz is grateful as well.

DR. KATZ: I'm sure he is. I have no conflicts of interest to report.

The ASTRO ETC paper that was originally promulgated September 2008 said that due to lack of peer-reviewed articles to support the use of hypofractionated stereotactic radiation, that they would conclude that it was a promising technology but not to be considered yet the standard of care.

What I wanted to share with the committee is that since that report, there is a significant amount of data now in the peer-reviewed literature and I want to go over that with you.

The first was Dr. King's study, which has been alluded to before, which came out in '09. Then Dr. Friedland and Dr. Freeman from Naples reported this recently, and then I recently published my cohort of 304 patients, which just came out in February.

The first, the King study is a Phase Two trial with 41 patients analyzed. They were

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low risk, all received CyberKnife therapy, and they received a dose of 36.25 gray, five fractions, some daily and some every other day.

At 33 months follow-up there were no failures reported, there will be an update actually for the committee from another physician later on on this paper with further follow-up. The PSA levels were very low, with 78 percent below the 0.4 number, and there was acceptable toxicity similar to other forms of radiation.

The Naples study came out, as I said, just recently. 112 patients, mostly low risk,

all received CyberKnife monotherapy, most received 35 gray in five fractions on a daily basis. Their median follow-up was 24 months. There were three failures, only two of them were local. There was less than five percent significant rectal or urinary toxicity. And 81 percent of the patients had potency preservation. This was recently updated in abstract form at ASCO and it remains 98 percent control at 30 months.

My study of 304 patients actually does include a fair number of intermediate risk patients and also approximately 12 high risk

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patients. They all received CyberKnife monotherapy. The first group of 50 received 35 gray in five fractions, and then the dose was escalated to 36.25 on a daily basis. Median follow-up in this paper was 24 months, but the initial 50 who received the 35 gray had a 30-month median follow-up. Overall biochemical disease-free survival was 98 percent. There was actually only one local failure and that was in a high risk patient.

Now with CyberKnife that was used in this study, four seeds were placed in the prostate and these were continuously tracked. For those of you on the panel who are not radiation oncologists, the prostate can move significantly both translationally and rotationally during treatment, and the CyberKnife allows us to track the movement of the prostate during the treatment and actually to automatically make corrections.

So one of the things that has been brought up about CyberKnife is that it can cause significant rectal toxicity. We've actually seen very low rectal toxicity, and I think some of that is due to the fact that we

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have such accurate placement of the beams, and we use approximately 150 beams on average. This also allows us, this accuracy allows us to use tighter margins, which I think is also responsible for low morbidity.

At 30 months the median PSA was 0.22, which I think is significant. At 42 months in a pending publication, I'm reporting a median PSA down to 0.11, which I think is extremely favorable when compared to other forms of radiation. The toxicity has been very mild, less than five percent in grade two or three rectal and urinary toxicity, and most EPIC scores have returned to baseline as you saw in

the Sandler study.
Potency preservation has also been quite favorable, slightly greater than 80 percent.
Now also pending, actually just accepted for publication is a paper that I gave with 75 patients using CyberKnife as a boost, very similar to the HDR brachytherapy model. These were intermediate and high risk patients. They got 18 to 21 gray over three days as a boost after 45 centigray to the pelvis. With

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36-month median follow-up we're seeing a 92 percent disease-free survival for intermediate risk and 80 percent at high risk. And based on what was shown previously, this seems pretty well in line with other forms of radiation, especially brachytherapy. There has been low urinary toxicity. We have seen some increase in rectal toxicity, which I think appears to be due more to the addition of the external radiation. The potency rate was approximately 78 percent. So these results seem to track most studies as noted in the paper with using HDR as a boost, both in terms of control and toxicity, and obviously we will be doing further follow-up and reporting on that as further follow-up occurs.
In summary, so far we're seeing very high rates of control. We're seeing extremely low median PSAs at this point, which I think according to the radiation literature is a good proxy for good long-term control. Compared to other forms of radiation, the toxicity appears to be as good if not even slightly better. We also are seeing high rates of potency preservation. And this is a very convenient

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treatment, only five days, and most patients are very grateful for being able to get their treatment done in five days rather than 45 days.
Thank you for your time.
DR. GOODMAN: Thank you very much, Dr. Katz, we appreciate that input. And then our final speaker, scheduled final speaker is Dr. Anthony Zietman, representing the American Society for Radiation Oncology.
DR. ZIETMAN: Thank you. I am Anthony Zietman, president of the American Society of Radiation Oncology. I have no conflicts. ASTRO represents 96 percent of radiation oncologists in the U.S.A., and bearing in mind all of the evidence you've

heard so far this morning I'm going to dispense with my slides, and it has been very nicely summarized, particularly by Dr. Sandler and Lee, who point out the high quality of evidence that exists with long-term outcomes. I'm going to make a few points and then for the panel's purposes I'm going to summarize the randomized trials that are out there at the moment that will be presenting

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their data in the near future, because this I think will factor into your thinking. I want to say something about active surveillance. ASTRO understands this issue, we recognize there is overtreatment, and it is at this moment a major research focus of many of the leaders of ASTRO. We write editorials on the subject and we discuss it at all of our major educational venues, including the annual meeting. And there has been evidence over the last five years that adverse events are actually on the rise again, so we have received the message. But we have to remember that prostate cancer is a spectrum of diseases from the mildest of run-ins to fatal at the other, with a huge gray area in between. And the patients exist on a spectrum also, from the cool at one end to the highly anxious at the other. So treatment is always going to be required. You have heard a great deal of evidence, there is no lack of evidence of the efficacy of radiation therapy, there is just a lack of comparative evidence, that is the deficit.

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You've heard from two speakers about the Scandinavian randomized trial published in the Lancet in 2009 by Widmark. It shows the survival advances in men with more locally advanced cancer. There is another randomized trial even bigger than that with 1,200 patients that will be presented at ASCO next month. The specific data is embargoed at present, but I can tell you that that will reflect the Scandinavian trial and I think that will be an important piece of evidence to consider. There are two randomized trials that you know about showing that the addition of radiation to surgery improves mortality, further proof of evidence that radiation cures patients with prostate cancer, and cures patients who need to be cured. You've heard about the randomized trials that show that cure

is increased by higher radiation doses, but high radiation doses need accurate delivery. Hence, the proliferation of technologies that lead us to this discussion today. It's actually a testament to U.S. creativity when it comes to technological problem-solving. And most importantly, you need to know

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about the mother of all randomized trials, I was on the steering committee of the trial in the U.K., it's called PROTECT. We've randomized a quarter of a million men to PSA screening or no PSA screening. Of those who have PSA screening, if prostate cancer is diagnosed, they are further randomized to surgery or radiation or active surveillance. There is no question about can this trial be done, it can, it has been, the last patient was randomized in January 2009, the first report will be coming out in 2015, which really is not so far away.

You heard a great deal about morbidity and function with various radiation treatments. I'm not going to add anything to that except to say that prospectively gathered data from thousands of patients regarding quality of life endpoints can't be dismissed lightly simply because it's not randomized. There's plenty of efficacy with low morbidity, just not much comparative evidence.

And finally, I would like to say something about this question about the evolving technologies, proton beam, SBRT,

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hypofractionation generally. All are incredibly intriguing. They are interesting technological solutions to our problems. There is long-term data, and you've heard it on proton beam radiation, less on the other kinds. You need to know that we are actually doing the studies that you will want to hear. There are three randomized controlled trials currently in motion looking at hypofractionation, one in Britain, one in Canada, and one here with the RTOG. All trials are close to completion. In total it's about 5,000 patients on trial, and we should have the first results within the next few years.

In addition, there are three randomized trials in evolution, or two randomized trials in evolution comparing SBRT with conventional radiation, and there's one other that's going on in Sweden that's also already 50 percent through its accrual. There

is another randomized trial comparing IMRT with proton beam radiation that is ready to go and is just awaiting federal funding, that's the Prosper grant and we're crossing our fingers.
DR. GOODMAN: About a minute and a
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half, Doctor.
DR. ZIETMAN: Sure. And finally, there are four separate efforts to develop national prospective prostate cancer registries, radiation registries to help supplement the randomized trials and answer the comparative effectiveness questions, so again, are waiting federal funding decisions. There's another that has been initiated by ASTRO with multiple stakeholders that has real momentum now.
So I will finish by saying I recognize that you have questions to answer today, but I would like to appeal for no hasty decisions. Ours is a field that has been compelled by the comparative effectiveness mandates and we are actually making an international effort to get our house in order and to answer the questions that you need. Thank you.
DR. GOODMAN: Thank you very much, Dr. Zietman, and we especially appreciate your ability to modify the format of your presentation given what has been heard thus far. We thank you for the news on ongoing trials. Of course our panel is interested in
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hearing those remarks and is also able to distinguish between a published randomized controlled trial that's been subject to peer review and one that has been discussed as an abstract, and those that are in the pipeline. We appreciate those distinctions, I am sure. Thank you to all of our planned and scheduled speakers.
Before proceeding, I failed to remind everyone in the room, if you've got a Blackberry, you might want to turn it off or down, and that applies to everyone, thank you. I have a list of, it looks like 15 nonregistered speakers, and we'll take them in the order in which they signed up. And just a couple of reminders, please. Wait until you come to the center mike before you start speaking, because our trusty court reporter would have a very difficult time in recognizing you and making sure he gets started on time. I apologize that we only have really a minute, truly 60 seconds from the time you

start until the time I have to ask you to finish, so I hope that you'll make sure that you will focus in on the essential points that

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you want to transmit to our group. And just so the people can think about when they're lined up, if you don't mind, I'm going to try, without butchering too many names, to just read down the list of people so that you can think about when you come in the order, and we will try to be efficient that way. My apologies for misnaming here.

Thomas Fogarty, Jamie Bearse, B-E-A-R-S-E, Don Fuller, Debra Freeman, Fred Kinder, Thomas Farrington, Douglas Hague, Scott Silverman, Paul Derby, Jan Fersing, I'm sure that's not correct, Gene Howard, Clinton Medberry, III, Mark Perman, Quinton Heim, and Greg Dickerson.

And if we could start with, it looks like Dr. Thomas Fogarty first, sir, welcome. Please remember to give your affiliation.

DR. FOGARTY: My name is Thomas Fogarty, I'm a cardiovascular surgeon, been accused of being an innovator, I have no affiliation. I do have conflicts of interest and they're noted on the form I filled outside. I would like to give you a perspective of an innovator primarily, an innovator in

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medical devices. People say the challenge to innovation is the development of the innovation. That's not true. In everything I've been involved in and others, the challenge is displacement of the old, not of the old technology, the old prospectus, the old attitudes and the old relationships. And if you look at what we're considering now, much of what we're considering is just these things.

So, I would like to mention the influence of societies. Societies represent their constituency primarily, but more importantly they represent the interests of the patients, and I think very often we forget about that. So, the presentation by one of the presenters really presented a perspective of the patients and I think it's extremely valuable in your considerations. Thank you.

DR. GOODMAN: Dr. Fogarty, thank you. Before you leave, the sign-up sheet shows your affiliation as with CyberKnife Coalition; is that correct.

DR. FOGARTY: Yes.

DR. GOODMAN: Thank you very much, I

appreciate the clarification. Jamie Bearse,
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please.
MR. BEARSE: Thank you for having me, good morning. My name is Jamie Bearse, I'm the chief operating officer for ZERO, the Project to End Prostate Cancer, a nonprofit located in Washington, D.C. We have been around since 1996 and we do an array of things toward trying to end the disease. We have a database of about 150,000 activists and advocates. We have a project that's called the Drive Against Prostate Cancer where we screened over 110,000 men for free.
We annually put on the Summit to End Prostate Cancer, where we bring in more than a hundred advocacy leaders from across the country to lobby staffers on Capitol Hill and congressmen and senators for increases in prostate cancer research funding. We manage a race series that's rapidly growing called Great Prostate Cancer Challenge. We work with more than two dozen large urology practices across the United States and our board includes members such as two-time World Series champion Ken Griffey, and Hunter Byden, who is the son of the Vice President.
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On behalf of all those people, I am here to implore you to not treat prostate cancer like there is a cookie-cutter treatment for all prostate cancer patients. What doesn't work for one man may work for another, and I've seen that. I've worked for ZERO for ten years now and seen many patients die from prostate cancer needlessly. For example, there was a woman that I spoke with yesterday morning whose husband died two years ago from prostate cancer, aggressive, at 52. Left behind three teenage daughters who --
DR. GOODMAN: Mr. Bearse, will you wrap up?
MR. BEARSE: Yeah. Who will not be dancing with their father when they have their wedding. The point is, there's no cookie-cutter solution to prostate cancer.
DR. GOODMAN: Thank you, Mr. Bearse, thank you for your comments, sir, we appreciate them. Dr. Don Fuller, please, is next, and he will be followed by Dr. Debra Freeman. Welcome, sir.
DR. FULLER: Thank you. Dr. Don Fuller on behalf of CyberKnife Coalition, and
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just by background, a radiation oncologist at a ten-physician single specialty group practice giving all forms of radiation. My virtual HDR CyberKnife study is referenced in the ASTRO ETC report. My only issue with that is it's out of date and out of context. It's presented as a small clinical study with short follow-up and that's really not the thrust of the study. The thrust of the study was to look at a dosimetry comparison with HDR brachytherapy versus CyberKnife, and it demonstrated that the CyberKnife device has the capability to deliver a substantially equivalent dose pattern both in terms of dose escalation with the extraurethral prostate as well as sparing of the urethra, the bladder and the rectum. And so it would be our position that HDR brachytherapy literature also supports SBRT literature. In a more simplified form, dose is dose. Delivering mechanism is irrelevant in my opinion.

DR. GOODMAN: Thank you. Dr. Debra Freeman is next. Welcome, Dr. Freeman. Please give your affiliation.

DR. FREEMAN: I'm Dr. Debra Freeman, I'm a practicing radiation oncologist in

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Florida, I'm here on behalf of CyberKnife Coalition, and I do consulting work for the clinical development department of Accuray. As Dr. Zietman referenced, and I want to mention that there is data forthcoming in addition to what you've heard about. There are two multicenter studies that data will be released within the next year, some at the upcoming AUA, with over 300 patients treated with CyberKnife SBRT for prostate cancer, so there is more data forthcoming.

In terms of randomized clinical studies, I want the panel to be mindful of the limitations of those studies in all aspects of what we do, particularly in regards to SBRT. I'm aware of one of the three that Dr. Zietman referred to that's been shared with the RTOG, and I think has not yet been approved, comparing two different SBRT regimens, a five fraction and a 12 fraction. That study alone does not even have a control arm of standard therapy, so it's two hypofractionated regimens, neither one of which is proven.

And in that regard, be mindful of the definition of SBRT, which in terms of the AHRQ

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report and I think most of Medicare is a hypo or extremely hypofractionated regimen of one to

five treatments. There are other forms of hypofractionated, low number of fractions of radiation that do not meet the definition of SBRT. Thank you very much.

DR. GOODMAN: Thank you very much, Dr. Freeman. Next is Fred Kinder. Welcome, sir. Your name and your affiliation.

MR. KINDER: Hi, thank you. I'm with the CyberKnife Coalition, I'm a prostate cancer patient, and I'm in the high technology field. So when I was diagnosed I researched every option, and CyberKnife, as many of you have heard today, dose escalation improves cure, so when I looked at the tracking capability of CyberKnife, being the only automated system, that was an obvious choice. I was treated by Dr. King two years ago, no side effects today, and my PSA is .5. I encourage you to authorize payment for the CyberKnife.

DR. GOODMAN: Thank you, Mr. Kinder. As he walks back I just want to remind our panel that this panel does not authorize payment or make a policy decision. We are to

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provide our expert consideration regarding adequacy of the evidence and what the evidence says. Thank you.

Next is Thomas Farrington. Welcome, sir, and can you please give your affiliation?

MR. FARRINGTON: Thank you. I am Thomas Farrington, I'm a ten-year prostate cancer survivor from Boston, Massachusetts. I am the president of the Prostate Health Education Network.

Following my combination brachytherapy and external beam radiation treatments in 2000, I focused on the African-American prostate cancer crisis. I authored my first book in 2001 and founded the Prostate Health Education Network in 2003. In 2009 I had recurrence of prostate cancer. It was initially decided that my best course of action was hormone therapy. However, while awaiting treatment I discovered CyberKnife. And my prostate gland was negative with the biopsy and it was determined that I had expression only recurrence, which made me a candidate for the CyberKnife treatment. I had three CyberKnife radiation treatments in July 2009 and in January 2010 my

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PSA had dropped from 2.5 to .2, where it remains today. My lower PSA has come with no treatment side effects at all. CyberKnife offered me a potential permanent cure and it

may be the only treatment available that can cure prostate cancer over metastasis. This unique treatment method should continue to be an option for prostate cancer patients where it can have an enormous impact. Most men with repression such as mine are not put on treatments that last a lifetime, with debilitating side effects, and overall they are much more costly than CyberKnife. Thank you.

DR. GOODMAN: Thank you very much, Mr. Farrington, we appreciate your point, and do call attention to the point you raised about representation of minority populations in the study populations. Thank you very much, sir. Next is Douglas Hague. Mr. Hague, if you'd give your affiliation, sir?

MR. HAGUE: CyberKnife Coalition. My name is Doug Hague. I'm a retired Superior Court judge in the state of New Jersey, I spent 30 years trying cases on the dark side, represented some patients, et cetera, but then

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I became a judge in New Jersey and I handled medical malpractice cases for most of that time in Madison, so I'm very familiar with disagreements among experts.

I was diagnosed in '03, found CyberKnife and was treated in '04. My current PSA is 0.04. I would just like to say that my quality of life is superb. I fish, I hunt, I have a 35-foot sailboat which I single-hand. And most importantly as far as quality of life is concerned, I really feel that I find the opposite sex absolutely enchanting. Thank you.

(Laughter.)

DR. GOODMAN: Congratulations. Dr. Scott Silver is next.

DR. SILVER: That's a tough act to follow. My affiliation is CyberKnife Coalition and my first comment is actually a question. Which men on this panel or in this room, if you were diagnosed with prostate cancer today, would choose watchful waiting or active surveillance to see if your prostate cancer spread locally or throughout your system before you decided to get treatment, particularly if a noninvasive painless procedure were available

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with little risk of adverse effects?

I am a board certified orthopedic surgeon who had to make that decision four years ago at the age of 61. My PSA had gone up 80 percent in 16 months, but was still below the level of four. I did extensive research to

learn as much as I could about prostate cancer and the available treatments. I spoke with patients and physicians throughout the country. I learned that the treatment itself can have a devastating effect on the quality of one's life.

The more I learned, the more I realized that I wanted to find a treatment that would offer me the least risk of erectile dysfunction and the best chance of a cure, one that would minimize complications and eliminate the possibility of incontinence. Doctors discussed the treatments with me. That can be overwhelming, even to a physician. But when the features of the CyberKnife procedure were explained to me, my decision became crystal clear.

In summary, I strongly feel that men with prostate cancer should have all the

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options available to them, and openly and honestly discussed with them.

DR. GOODMAN: Thank you very much, Dr. Silver, we appreciate your input. Next is Paul Derby. Mr. Derby, your affiliation, sir?

MR. DERBY: Yes. I'm here with the CyberKnife Coalition. I'm a computer scientist, I knew nothing about the medical profession until I was diagnosed with prostate cancer in August of last year. I asked my urologist if it would make any difference if I was treated in six months or eight months, I needed to do my homework. I did a huge amount of research and learned a lot about lots of options, and no one from the medical profession could steer me, I had to make the decision, and it was overwhelming. I had friends that had been diagnosed and they had suffered with a lot of various side effects, incontinence, multiple surgeries, things of this nature through prostate cancer.

I stumbled on to CyberKnife, it was fairly unknown. I was lucky to have a CyberKnife treatment center nearby and evaluated that with the other options and chose

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that. I'm 14 months now past CyberKnife. My PSA is the lowest it's ever been, it's .9, which is right where it should be, I expect it to drop. I went to work every day during the treatments, I suffered no quality of life impact, I'm delighted that I discovered this and I hope each of you males on the panel and the loved ones of the female on the panel have

that same option and know about it.
DR. GOODMAN: Thank you very much, Mr. Derby, we appreciate your comments. Next is Jan Fersing, I apologize if I'm mispronouncing your name, and your affiliation, please, sir.
MR. FERSING: My name is Jan Fersing, I'm here on behalf of the CyberKnife Coalition. I was treated by CyberKnife last August. And I live in Fort Worth, Texas, where Medicare does not approve CyberKnife for prostate cancer treatment, and so I got the treatment by offering to pay for it myself, and I'm through the long tortuous appeal process, I'm probably a step five now and it's still ongoing. But for me as an owner of a privately held company in Fort Worth, I had five or six stockholders. One of them died of prostate cancer

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complications. The second one was treated by proton at Loma Linda, his cancer returned, and he died. So watchful waiting was not an issue for me. I chose a treatment that I could do outpatient, five outpatient treatments. I could resume my normal active retired life. I had side effects, everyone has side effects. They disappeared after two or three weeks. Now my PSA is going down and I don't have any side effects. I'm here as an advocate for Medicare change in Texas that will allow Medicare treatment of prostate cancer by CyberKnife.
DR. GOODMAN: Thank you very much, sir, we appreciate your comments. Next is Clinton Medberry, our next speaker, and Dr. Medberry will be followed by Mark Perman, and then Greg Dickerson, so Greg Dickerson to follow Mark Perman. Dr. Medberry, welcome, sir.
DR. MEDBERRY: Hi. I'm Clinton Medberry, a radiation oncologist in Oklahoma City, and I'm president and chairman of the board of the CyberKnife Society. Oklahoma is a rural and a poor state, and men to get

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treatment there may have to drive as much as 120 miles each way every day to get radiation treatment. So what that means is if they can get four or five treatments with CyberKnife stereotactic body radiation therapy they can get treatment; if they have to get IMRT it simply is not possible for them, so men are having to choose not to get treated right now in Oklahoma. Men on the opposite side of the street in Texarkana have different choices

available to them. So I think this should be as a matter of fairness, that all the states should cover this like the 37 that do. The other point is that to get randomized trials and everything is going to take 15 years, and by then we won't be using any of these technologies in all probability, so I don't think we can wait on randomized trials in everything we do. Thank you.

DR. GOODMAN: Dr. Medberry, thank you. Could you remind me what your affiliation was, I'm sorry, I didn't catch it.

DR. MEDBERRY: I'm president and chairman of the board of CyberKnife Society, and also on the board of the CyberKnife

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Coalition.

DR. GOODMAN: Thank you, sir, we appreciate your comments. Dr. Mark Perman is next. Yes, sir, welcome, and your affiliation?

DR. PERMAN: Hi. My name is Dr. Mark Perman, I'm a practicing radiation oncologist in Florida and also serve as the president of the Florida Robotic Radiosurgery Association, a group of nine community radiosurgery centers. In October 2009 First Coast Service Options, the Florida Medicare intermediary, released an LCD on stereotactic body radiation therapy. While not included as a covered indication, the LCD did state that prostate cancer radiosurgery could continue for appropriate patients. Additionally in its comments, the medical director wrote that patients enrolled in a registry would be looked upon favorably when being considered for payment. In response I set about developing a mechanism that would address evidentiary gaps and fulfill the requirements of the LCD. We have chosen to open a prostate SBRT registry with patient accrual beginning in June 2010. The registry will be treatment platform neutral

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and is designed to track toxicity as well as treatment outcomes. The information collected in our registry will allow Medicare beneficiaries throughout Florida continued access to prostate SBRT as well as to provide important data on the responses to this type of radiation treatment.

DR. GOODMAN: Thank you very much, sir, we appreciate those comments. Next is Greg Dickerson. Your affiliation, please?

DR. DICKERSON: I am Dr. Greg Dickerson, from Denver, Colorado. I'm the

medical director for Denver CyberKnife, and the practice is limited solely to CyberKnife radiosurgery. I'm speaking on behalf of Dr. Chris King, currently at UCLA, on his update of Stanford University Experiencing Stereotactic Body Radiation Therapy for the Treatment of Low Risk Prostate Cancer. Since the original publication of this data in 2008, a total of 69 patients have been treated with two years or more follow-up, bringing the current median time of follow-up to 3.9 years. Only two patients have had biochemical recurrence which was biopsy proven.

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There have been no grade three bladder toxicities, three percent grade two toxicities, 24 percent grade one toxicities. There were no grade two or three rectal toxicities and 20 percent had grade one symptoms. Five-year Kaplan Meier PSA response relapse-free survival rate is now 97 percent, and I will provide copies to the panelists. Thank you very much.

DR. GOODMAN: Thank you very much, sir. I wanted to clarify something. I inadvertently skipped Mr. Gene Howard on the list, and Mr. Quinton Heim will not be reported. So that's the changes. Pardon me, Mr. Howard, and could you give your affiliations, sir?

MR. HOWARD: CyberKnife Coalition. As a World War II veteran, I believe that freedom is one of our greatest strengths. As president pro tem of the Oklahoma Senate and later as chairman of the Oklahoma State and Education Group Insurance Board, I learned that medical cost containment is necessary for affordable health care. Out of these and other life experiences, I believe that patients should have the freedom to make the final decision on

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their treatment subject to certain limitations: Treatment has FDA approval; cost of treatment is competitive with other options; and the patient has made an informed decision based on the best attainable information.

After my biopsy confirmed T2 treatable prostate cancer, I did extensive research, including consulting a number of specialists in Tulsa, Oklahoma. I also contacted the Proton Center in Oklahoma City and the HIFU Maple Leaf Clinic in Toronto, Canada. Concerning my quality of life and future I chose CyberKnife. I was shocked to find that my state, Oklahoma, is one of 13 where Medicare does not cover

CyberKnife, but they cover proton at about twice the cost. I still believe in my right to make an informed decision as to my treatment and not have it affected by economic or philosophical disputes. After all, this is my health and quality of life that I'm deciding, and I have to live with the consequences. Thank you for this opportunity.

DR. GOODMAN: Yes, sir, thank you, Mr. Howard, and thank you for your service as well, sir. We have an additional nonregistered

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speaker, it's Dr. Todd Wasserman. Sir, if you could state your affiliation, please?

DR. WASSERMAN: Todd Wasserman, professor of radiation oncology, Washington University. I have been involved in the leadership of the RTOG since 1973 and currently cochair the RTOG Foundation.

The Tufts group correctly concluded that there is insufficient data to prove the benefit of RT over active surveillance or watchful waiting, but they failed to discuss that the same lack of data does not prove the null hypothesis that RT is only as good as active surveillance or watchful waiting. They also concluded that higher radiation doses improve rates of long-term biochemical control. Chemologically there is no logic to this unless RT is having an effect, albeit yet unproven.

DR. GOODMAN: Thank you very much, Dr. Wasserman, and thank you for making that point. Ms. Ellis, I believe that's the completed list of nonregistered speakers.

MS. ELLIS: Correct.

DR. GOODMAN: Panel, I think we just

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heard from 15 of these speakers, and I know that, just speaking for the panel, we very much appreciate this diverse and important input from stakeholders, including many patients with many perspectives. I'm sure the panel may also have noted that the distribution of affiliations may not have been a random selection of people that may have been affected by these technologies, but we do appreciate the individual comments made by every single nonregistered speaker. Thank you, and thank you for trying to keep your comments to one minute. I know that's very difficult.

Well, let's proceed then. And as noted earlier, we're very glad and grateful that the speakers from Tufts EPC, our scheduled

commenters, and probably nearly all of our unscheduled commenters remain in the room. And what we want to do now is have some time for questions to presenters by the MedCAC. You probably want to focus primarily on the Tufts people and the scheduled presenters, but this does not mean that you are limited to asking questions about others.

I want to call attention to the fact,

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panel, that we do have a set of questions to answer later on, and these are voting questions, and to the extent that your questions can focus on and keep us on track with regard to addressing those specific questions, that will be time well spent.

So, with that, we'll open it up.

Dr. Jarvik is first, followed by Dr. McNeil.

And by the way, could the Tufts folks come up to the front, I believe those chairs were reserved for you, those are the hot seats, and I hope that other speakers will be hovering near the front of the room as needed. Dr. Jarvik, thank you, sir.

DR. JARVIK: My question is actually for Dr. Ip. With regard to the study by Widmark that was published in 2009, I think that was one of the studies you excluded from your review.

DR. IP: Yes.

DR. JARVIK: And I'm wondering if you could talk a little bit more about that. There was a mixture of T stage.

DR. IP: We excluded it because that study explicitly compared hormonal therapy with

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radiation therapy compared to just hormonal therapy, that was the reason.

DR. JARVIK: Okay. And the subfraction of patients that were T1 and T2 you didn't even look at, because the primary question was different?

DR. IP: Right.

DR. GOODMAN: And I'd just add that EPCs tend to stick with their assignment. Dr. McNeil.

DR. MCNEIL: I have a question for Dr. Dvorak and perhaps Dr. Lee. A number of analyses had varying degrees, varying years of follow-up for mortality or side effects, and I would like to ask both of you actually, if you had a T2 patient at medium risk and you wanted that patient to make an optimal or a well informed decision, how many years of follow-up

would you like for data in terms of mortality?
DR. DVORAK: I think I would defer this question to Dr. Lee.
DR. GOODMAN: Thank you. Dr. Lee? That was Dr. Dvorak, by the way.
DR. MCNEIL: You are a radiation oncologist, right? So I would like your answer

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as well.
DR. GOODMAN: As per Dr. McNeil's request, Dr. Dvorak.
DR. DVORAK: Very well.
DR. MCNEIL: I was specifically trying to get my answer from a practicing clinician in the field.
DR. DVORAK: So, I think to some degree this depends on the expected survival of the patient.
DR. MCNEIL: At 65.
DR. DVORAK: And again, this is a question of competing comorbidities.
DR. MCNEIL: With intermediate risk. I'm really trying to get a prototypical question here.
DR. DVORAK: Right. The NCCN guidelines stratify in terms of their recommendations patients based on their expected survival, and I think that's an important question. Having said that, I think ideally, because it's on average a slow moving disease, longer survival would be better than short survival, or median survival would be better than shorter.

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DR. MCNEIL: And what is median?
DR. DVORAK: I think ideally I would like to see ten years.
DR. MCNEIL: And Dr. Lee.
DR. LEE: I would agree with Dr. Dvorak on that. We have to keep in mind with intermediate prostate cancer we tend to bend it into one group. The reality is the heterogeneity of outcomes in that group is pretty diverse. For example, there's well published data stating that if you have only one intermediate risk factor versus having two or three, that your outcomes are quite different, but they're all considered intermediate risk. And I think ten years minimum would probably be adequate, maybe not for survival actually, because if you actually look at one of the observation studies from Johannson looking at it, it was a pretty comprehensive population-based study done in

Sweden, they followed over 200 patients with complete follow-up, so no patient was lost to follow-up and they followed them to their time of death.

It wasn't until after ten years,

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closer, getting into 13 or 15 years where they saw a dramatic drop in survival related to prostate cancer, so they're seeing a lot more of that after that ten-year mark.

DR. MCNEIL: Could I follow that up with one further point?

DR. GOODMAN: Of course, Dr. McNeil.

DR. MCNEIL: So I guess to anybody in the Tufts group, it strikes me that a large number of the analyses that you included for mortality and side effects and whatever had follow-up periods that were quite short. And the question I would ask is offhand, without being totally type A about this, what percent of your patients or your studies would drop out if you took a median survival of ten years?

DR. GOODMAN: Dr. Ip, could you venture a response?

DR. IP: No comment. I don't know.

DR. MCNEIL: Well, you must have some idea.

DR. IP: I have no comment.

DR. GOODMAN: Dr. Ip, if you and your colleagues might have opportunity to do a quick survey of the literature, maybe even during

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lunch, if you could give us some rough idea for that, that might be useful. Dr. Fischer is next.

DR. FISCHER: I'm also going to ask a question about follow-up, but it is really provoked by some experiences with my own patients. I'm a surgeon, but I have a lot of elderly friends as I get older, and it does seem as if the incidence of what proves to be radiation cystitis seems to increase with age. And I'm just wondering about the follow-up for this particular, what I consider a side effect of radiation, wherever it comes from. How long is it followed by the radiation community and put down or noted as a complication of the therapy?

DR. GOODMAN: Follow on in radiation. Dr. Lee is approaching the microphone and if someone else has a specific response, we will accept that as well. Dr. Lee.

DR. LEE: Good question. I would say in the GU toxicity profiles, when we start

classifying things as grade two and grade three, radiation cystitis is put into there. In general, there have been several reports,

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some including prostate cancer, some in the GYN literature stating your exact point, that potentially some of the radiation-related side effects to the bladder may take many years to manifest. Having said that, I think most of the time you're probably capturing most of those events somewhere between about five to ten years, and most of the dose escalation studies now with higher doses of radiation have exceeded that time interval, and the GU toxicity rates seem to be relatively constant after that time. The other point to keep in mind is that with hypofractionated regimens we don't know the answer yet but we do need to be careful, because in general one of the basic radiobiologic principles is that if you give higher daily doses of radiation, that you are potentially increasing the chance for having a late side effect many years down the road. That may or may not be the case with some of the modalities that we're discussing.

DR. FISCHER: Just stay there for a minute, please. And the only reason I ask that

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is because looking at the numbers that Dr. Dvorak and everybody else put up on the screen, it does seem to me anecdotally that the incidence of late radiation cystitis, very much as you said, and these are pretty much people I see for other reasons but happen to mention that they have this kind of symptomatology, is far in excess of three percent. And I'm just wondering who's logging that in, and we'll discuss that later on this afternoon, I hope, who's logging that in as a complication of a treatment.

DR. GOODMAN: Dr. Lee, is that being recorded appropriately?

DR. LEE: I feel in general it is. Certainly in our institutional database we do log that in. For the grade three side effect profile it's a matter of severity, so for example, people could have cystitis type symptoms, slowing of their urinary stream, urinary irritation, and they could be taking an alpha blocker, and in some series we would typically consider that a grade two side effect. So it does require some medical

intervention but maybe not too serious.
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Other centers, they routinely put patients on Flomax even before they start any definitive local therapy, so it's kind of hard to tease that data out.
DR. GOODMAN: Thank you, Dr. Lee. Dr. Hevezi.
DR. HEVEZI: Dr. Lee, would you return, please? I'm sorry to keep picking on you, but also this may be for Dr. Dvorak. Even though you gentlemen are a little bit younger as radiation oncologists and IMRT has been around now for ten years since it began its reimbursement around 2000, do you think if we held IMRT to the same level of evidence that we're holding some of the other new technologies, that we would have treated as many patients with IMRT as we have over the years?
DR. LEE: Without any absolute data, this will be a matter of only opinion. The number of IMRT cases probably would not have been perhaps as ubiquitous as it is now. That's not to take away from the fact that we do feel that it is a good treatment. And the reality is, one of the reasons why probably a
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number of medical technologies continue to propagate is independent of reimbursement. I think most physicians want to do the right thing for their patients, so if it's not working with a low side effect profile, they're going to stop. I mean, really it's not worth continuing on something like that, and so I think that's one of the main reasons IMRT has continued to do well.
We also have to keep in mind that even though background prevalence of prostate cancer is high and IMRT is used for it, IMRT, just like a lot of other technologies, has made substantial strides in a number of other disease sites. And you know, one thing we can take away is that if you've got prostate cancer, the people in this room probably do a good job taking care of you.
DR. GOODMAN: Thank you, Dr. Lee. Before we move to Dr. Potters, I just want to remind the panel that the things we care about most today as per our task include the adequacy of the evidence and what does the evidence say. Dr. Potters.
DR. POTTERS: Right. So in the
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context of the questions that were asked and the differing definitions of watchful waiting, expectant management and such, and given the previous answer of a ten-year mortality, and given the fact that a lot of these technologies are short of that, I would like Dr. Olsson to discuss the randomized trial on radical prostatectomy versus watchful waiting in the context of the outcomes of that trial, the definition of watchful waiting as it may pertain to the questions that we're being asked, because of, the outcomes of that potentially being a surrogate or a pivot point from which other definitions of outcomes can be utilized to assess the technologies that we're being asked.

DR. GOODMAN: Thank you, Dr. Potters. Do remind us at what point, where is that trial in the pipeline?

DR. OLSSON: That's already been done.

DR. POTTERS: This is radical versus watchful waiting.

DR. OLSSON: This is the Scandinavian Group Four study.

DR. GOODMAN: Reported in '09, was it?

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DR. OLSSON: Reported in I think '09, yeah, in the New England Journal as I recall.

DR. GOODMAN: Okay.

DR. OLSSON: What that did is randomize 700 men to let's say 350 and 350 essentially, for watchful waiting, which meant no therapy, there was no surveillance, to therapy. Keep in mind that the patients who were diagnosed here were actually not PSA diagnoses, these were real cancers, okay? And what it showed was that after eight years, by any measure you wanted to apply to the study, the cumulative mortality, the incidence of metastases, the incidence of progression was favored by the surgery group statistically significantly overall.

DR. GOODMAN: Thank you, Dr. Olsson. Dr. Potters, did you want to respond, or what would we take home from that exchange?

DR. POTTERS: You know, in the context of surrogate definitions, and we heard a lot of data, and maybe Dr. Sandler wants to talk about PSA outcome as a surrogate for after radiation therapy, that if we compare radiation literature to surgical literature, and even if

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we show an evenness, and Dr. Grimm showed the data that surgery, radiation, seeds were about

the same, that there could be a crosswalk that could be made that looks at mortality using a PSA surrogate outcome, which is not really what the Tufts people looked at.

DR. GOODMAN: Right, so that was not within their realm, but that would certainly be an indirect comparison at best.

DR. POTTERS: Right, so maybe Dr. Sandler wants to --

DR. GOODMAN: Is this a relevant point now, to ask Dr. Sandler?

DR. POTTERS: Yeah, I think so, because it will just continue in the context, unless the panel is satisfied.

DR. GOODMAN: Dr. Sandler, why don't you come up and address that.

DR. SANDLER: Thank you. The issue I think, Dr. Potters, had to do with the surrogacy of PSA failure. I cannot say as a clinical trial that PSA failure has been reversely assessed in a definitive way as a surrogate endpoint.

However, as Dr. Lee mentioned,

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biochemical failure has important clinical consequences. Patients who fail biochemically often go on to other treatment such as hormonal therapy, which can have a big impact on quality of life, so biochemical failure is a clinically important endpoint.

DR. GOODMAN: Clinically important, may not be a perfect surrogate, however, for the outcomes about which we care today.

DR. SANDLER: Yes.

DR. GOODMAN: Thank you.

Dr. Schwartz.

DR. SCHWARTZ: I had two questions, one of which really dealt with the surrogate proxy issue, in part because of the question that Barbara asked before, I would just note that I think in looking at, you know, in theory there's no difference between theory and practice, but in practice there is. And so we're interested in long-term outcomes, and not many of them have long-term outcomes in a technology that's constantly changing, so we need to think a lot of about this.

The other question that relates to that, though, has to do with side effects. And

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you know, we know from recent press reports and other things that there are errors made in practice, and particularly with radiation therapy there have been a lot of the reported

errors in planning and in, you know, equipment failures or algorithm failures or things like that. I just wonder if any of the speakers, we've heard that one of the technologies automatically monitors the position of the prostate. I just wonder if there is any evidence that there are fewer failures or fewer side effects from any of these modalities because of the actual implementation of the technical aspects as they relate to side effects.

DR. GOODMAN: Thank you, Dr. Schwartz. It is relevant to the extent that we've been asked to look at adverse effects, and I concur, I don't believe we've heard any discussion about those kinds of potential causes of adverse effects.

DR. SCHWARTZ: And so I wonder if there's any evidence, I know what theory would say, but I just wonder if there's any data out there.

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DR. GOODMAN: Yes. This is Dr. Zietman approaching the microphone. Briefly, Dr. Zietman.

DR. ZIETMAN: I will certainly address this as the president of ASTRO. We are very aware of this risk for errors. Radiation is a great treatment but it also carries its risks, just like the knife, and with increasing complexity of treatment there will be increasing risks. So at the specialty level we are trying to change our culture to one that compares with the airlines, so there's going to be a very strong safety culture that will hopefully catch any such errors.

DR. SCHWARTZ: And Anthony, before you leave, do you know of any data that suggests that there is any difference in propensity to error right now of the major technologies? I mean, we've had brachytherapy problems. Is there any data or evidence to suggest that one of these treatments is more likely, or some are more likely than others?

DR. ZIETMAN: There is not.

DR. GOODMAN: Thank you, sir. This is Dr. Collins approaching the microphone?

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DR. FULLER: No, Don Fuller.

DR. GOODMAN: Oh, Dr. Fuller, pardon me.

DR. FULLER: Just at least theoretically, if you're continuously tracking the target and have a mechanism that

continuously adapts the aiming, you can use a smaller margin. And I think radiobiologically, there's no question that the smaller the volume you're treating, the lower the risk of complications. It's impossible to prove from the literature, it's new technology.

DR. GOODMAN: Thank you, sir.

Dr. Satya-Murti was next, I believe.

DR. SATYA-MURTI: We were debating biochemical failure and I'm impressed by the definition, that even that is variable as to who defines the biochemical failure. Is that an absolute drop to a cutoff point or is it a percentage drop, and then over what period do we determine that there has been a biochemical failure? Because in the absence of actual mortality we are hinging quite a bit of our conclusions on biochemical failure, whereas that in itself is a consensus, and I'm not

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convinced that carries as much internal validity.

DR. GOODMAN: Yes, Dr. Sandler.

DR. SANDLER: So, Dr. Satya-Murti, I either get the credit or the blame for the Phoenix definition, which is the nadir plus two definition, I was the one who organized the Phoenix conference that came up with that definition. And the reason that we defined nadir plus two with a multispecialty consensus panel was briefly that after radiation therapy, there can be benign fluctuations in PSA, and we did using a receiver operating curve analysis find that nadir plus two gave us the best ability to pick up clinically important biochemical relapses. Nadir plus one, a smaller value picked up too many clinically unimportant, and nadir plus five or six was overkill in terms of sensitivity in detecting clinically important failures.

DR. GOODMAN: Follow-up, Dr. Satya-Murti?

DR. SATYA-MURTI: That explains why you chose that. Much like the tumor markers of the past, like AFP, we have learned that they

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are indeed prone to errors, including false positives. So how do we know that this rise itself equates to tissue breaking through the prostate capsule, or eventually marks a worse prognosis?

DR. SANDLER: We used several large data sets that were analyzed comprehensively by a biostatistician at M.D. Anderson to generate

the receiver operating curves with a nadir plus definition, we looked at multiple definitions. Nadir plus two was the one that was most closely associated with downstream clinical events that would be a consequence of prostate cancer relapsing, either distantly or locally.
DR. SATYA-MURTI: Very last, this is brief. Do the surgeons and watchful waiting proponents agree with this definition?
DR. SANDLER: So, surgery is generally different than radiation in terms of what the biochemical failure rates are and basically any detectable PSA after surgery is a surrogate for prostate cancer being present. For watchful waiting, as I said in my talk, there's not well accepted standards for what failure is, although most commonly it's the slope of PSA in

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a watchful waiting setting that is used to generate a recommendation for a definitive treatment.
DR. GOODMAN: Thank you, Dr. Sandler. Dr. Dmochowski is next.
DR. DMOCHOWSKI: Dr. Ip, looking at, go back to the toxicity questions. I presume that you accepted authors' or articles' definition of reported toxicity as what you were reporting, you didn't superimpose some sort of overriding taxonomy on the adverse outcomes reporting, or did you?
DR. IP: No, we did not. The only thing we did was because a lot of the studies, like for example they would report RTOG grade one, two, three, four. To simplify our summary we basically used grade three or four to summarize that particular study, so we didn't summarize a grade one and two.
DR. DMOCHOWSKI: Because I notice at least in one of your slides you actually used symptom analysis and seemed to lump that into a symptom score.
DR. IP: Yeah, we were just reporting what the study recorded.

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DR. GOODMAN: Dr. Dmochowski, what's the point to be taken from your comment, or observation?
DR. DMOCHOWSKI: Well, I'd like to sort of chime in to what Dr. Fischer mentioned. I have concerns regarding some long-term effects and I want to pre-specify that I no longer treat prostate cancer, I've not done it for ten years, my practice is solely a female practice because my specialty is pelvic

reconstruction. And one of the areas that we, at least in the Tennessee area are seeing a lot of, is radiation injury from gynecologic radiation for malignancy 20, 30, 40 years down the line, not ten years, not five years. Now I realize, and pertinent to what Dr. Schwartz mentioned, one of the things we're being asked to do is capture a moving picture of a variety of interventions and sort of the downstream effects of those interventions. So it's not clear at all that we're looking at a united front, we're looking at quite different interventions. And my concern is we really are talking a lot about efficacy, but from a patient standpoint, curative cancer is

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miserable because of a destroyed urinary or lower GI tract is not acceptable for patients, and we see this a lot on the benign side for various interventions. So my concern is that we don't lose sight of the fact that we really, and this isn't an indictment of the medical literature, but we have poor taxonomies for outcomes reporting subjective and objective, and specifically regarding genitourinary and gastrointestinal, and we must come to global consensus across the specialties, radiation oncology, medical oncology, urology, all those who deal with prostate cancer, in terms of having some common language for purposes of being able to compare data and for comparative effectiveness search.

DR. GOODMAN: Thank you, Dr. Dmochowski. You may want to remind us of that toward the end of the day when we identify potential gaps in evidence. Dr. Fischer and then Dr. Mock, and then Dr. McNeil. Dr. Fischer.

DR. FISCHER: I hadn't wanted to, but Dr. Dmochowski had reminded me that what I do is basically gastrointestinal cutaneous

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fistulas and reoperative surgery. And there is an entity, mostly from gynecological radiation, of the dead pelvis. This occurs about 20 years and it will erode into the bowel and give you a terrible gastrointestinal cutaneous fistula generally draining through some natural orifice, and what one has to do is basically fix the bowel.

But the other thing you have to do is take the bilateral gracilis flap, the gracilis muscle on either side and put it in either through the old vagina or a neovagina and then

align the pelvis, which is absolutely dead, there's no muscle, the bone is in terrible shape, and then get a blood supply, and then you can resect the bowel and then put it down on this living tissue. It doesn't occur very often, but it does occur.

I wanted to ask a question in follow-up to Sandy Schwartz's question and that is when a patient undergoes radiation therapy, there's a radiation physicist who theoretically calibrates the machine, I don't know whether they calibrate it that day or on a particular patient or once a month or whatever.

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Dr. Dvorak, you showed some very nice slides about changes, I think it was you, where the prostate is, and it may change, bladder fills up, rectum full of gas. Who calibrates that? I mean, you've shown that it varies, and presumably the dose will vary at given times. Is there anyone who calibrates that or worries about that?

DR. GOODMAN: Dr. Dvorak, you might be able to answer that, but if someone actually does this, and I see Dr. Lee might be able to supplement that. Dr. Dvorak, anything on that?

DR. DVORAK: So, I would just say that our review of the evidence has not specifically discussed any of the technical issues, and I would defer to Dr. Lee in terms of more comments.

DR. GOODMAN: Thank you. Before we go to Dr. Lee, Dr. Hevezi I think has some expertise in that area.

DR. HEVEZI: Yeah, I am a medical physicist working in radiation therapy physics for the last 30 years, and I would say that some of these effects that you gentlemen are speaking to may have been done by older

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radiation therapy technologies, and you're seeing sort of the result of that. I think our newer technologies now, we are aware of many of the kinds of toxicities that may occur, and so our new procedures are designed to sort of avoid those kinds of things. But I agree, we need to come up with some kind of format to describe these as we go forward.

DR. GOODMAN: Thank you. Anything to add, Dr. Lee?

DR. LEE: I would echo those comments. Keep in mind 20 or 30 years ago, none of the treatment modalities that were presented were probably being used. GYN, oftentimes it's just

an anterior-posterior beam, the exposure to the entire bladder and bowel is significantly higher, In addition to that, if they received an endocavitary implant for cervical cancer, for example, yes, there could be some morbidity associated with that.

As far as prostate cancer is concerned, more and more we're trying to get away from physician-reported side effects. We're more interested in if the patient does have a side effect, how is it affecting their

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quality of life, so we're moving more toward patient-reported quality of life data as you can see here.

Regarding the piece about who's monitoring the position of the prostate and that sort of thing, you know, it was actually a little bit underrepresented in our presentations, but that's what image-guided radiation therapy is all about. We have one radiation oncologist who's been around a long time and who says one of the greatest advances in radiotherapy was the back lock immobilization bag, because that insured that the patient got on the table in a reasonably consistent manner, so that was step one.

The other thing most centers I think do when they're giving external beam radiation is that they put in radiopaque fiducial markers inside the prostate and that's what allows the realtime tracking or the image guidance up front so that you can use a tighter margin and treat less tissue.

DR. GOODMAN: Thank you, Dr. Lee. I want to just curtail the discussion on this topic, if I may. We can come back later if

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necessary. The point was well taken, raised originally by Dr. Schwartz that, how these radiation therapies are implemented and under what levels of quality control is important.

I'd also note that I don't think we've heard any evidence or studies on that today, and that does not mean that's an irrelevant subject because we are asked to look at adverse events, so I very much appreciate that that point was raised.

We also appreciate that this is a bit of a moving target problem.

Some of the morbidities and effects that Dr. Fischer mentioned are the result of applications done years ago but that is still the real world and we are still in search of

good evidence on those issues and we wish it had been generated earlier, to tell you honestly.

I want to move to Dr. Mock and then Dr. McNeil. Dr. Mock.

DR. MOCK: Thank you, Dr. Goodman. I want to shift a little bit down toward the higher numbers on the question scale, specifically regarding generalizability. As we

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talk about the geriatric population and those in the CMS and we also talk about community focus, I have been quite moved today by some of the testimonials of the CyberKnife patients, but I don't have, and I'm not sure anyone else on the panel has a feeling for really where are we today with treatment. Where is and what is access to really quality affordable cancer care in our communities?

I did hear someone say that well, they went 120 miles for treatment and that that wouldn't have been available at his home. I'm not sure if Dr. Zietman or who, I'm not going to implicate anyone, but I would like to have one of you specialists please tell the panel as we are today, is IMRT community available? Is the treatment that's been referred to, called CyberKnife, is that something that is only localized in the population centers of the south? Please give us an idea of what is available, as is, for quality affordable cancer cure and care for those possibly that are elderly and have resource constraints and transportation constraints to get to treatment.

DR. GOODMAN: Thank you, Dr. Mock, but

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before proceeding, remind at least me why that's relative to our evidence questions, can you be more specific why it's about evidence?

DR. MOCK: Our last question on our list of questions is whether or not this is generalizable for the CMS population, that's number one, and whether or not this is generalizable to the community.

DR. GOODMAN: Thank you, Doctor. I believe Dr. Wasserman has a response.

DR. WASSERMAN: Right. Speaking for the RTOG, our last two completed prostate trials which entered over, about 2,500 patients, the median ages for those trials were over 67, one was 67, one was 69, and about two-thirds of the IMRT that's given is given by community centers.

And I would like to just comment on

Dr. Dmochowski's issue about scoring.
DR. GOODMAN: I'm sorry,
Dr. Wasserman, not at this time.
DR. WASSERMAN: Thank you.
DR. GOODMAN: Is this Dr. Medberry?
Yes, sir, Dr. Medberry.
DR. MEDBERRY: Yes. On the east and
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west coast, I think IMRT is generally available
to most people reasonably conveniently, but
when you get into the interior of the country,
particularly rural states like Oklahoma, Texas,
Nevada, Montana and so forth, it is not. So
for a man in Oklahoma to be able to get IMRT,
he may have to drive literally 120 more miles
each way every day for over 40 treatments, and
that's just simply not fiscally possible for
our Oklahoma patients.
DR. GOODMAN: Thank you, Dr. Medberry.
Dr. Mock, is that sufficient for now, sir?
DR. MOCK: Yes, thank you.
DR. GOODMAN: Okay. If it's on this
point, Dr. Potters, then yes. If not, we'll
move to someone else.
DR. POTTERS: As a practicing
radiation oncologist, I just would like to
remind the panel that from an access
perspective you could do prostate
brachytherapy, which is a single treatment
modality. So from a travel perspective and
access, that represents a competing
opportunity.
DR. GOODMAN: Thank you, Dr. Potters.
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Dr. McNeil is next.
DR. MCNEIL: I just have one comment,
and somebody can address this if they wish. In
looking over the questions, most of them relate
to the adequacy of the evidence, and in fact to
answer those questions we're looking at the EPC
report. In an earlier question and an earlier
comment the Tufts group indicated that they
hadn't summarized the data from the various
clinical trials in the forest plots because of
the heterogeneity within the trials within the
various plots. I would suggest that maybe
those plots are misleading in that when we're
thinking about these questions, if in fact
those data cannot be aggregated, then in fact
it's not fair to put them all on the same plot.
DR. GOODMAN: So Dr. McNeil, you're
saying that really they are more heterogeneous
than might be expected given that they appear
on the same sheet of paper.

DR. MCNEIL: That's exactly what I'm saying.
DR. GOODMAN: Point well made. I believe it's Dr. Samson and then Dr. Schwartz.
MR. SAMSON: Okay. A couple of
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questions, first directed at the Tufts group, and this refers to the presentation by Dr. Grimm earlier. Your work was really focused on direct comparisons of randomized trials and nonrandomized comparative studies. Dr. Grimm's presentation was on indirect comparisons, these were all single intervention studies, and the selection criteria used in Grimm's report was those articles stratifying patients by risk. I just wanted to get your reaction to that approach, the idea that they at least tried to control for some of the heterogeneity among these groups.
But I also wanted to point out that the outcomes that they were looking at were PSA progression, and I'm sure that across these studies it was defined in a variety of ways. Do you have any response to just the approach that was used in that study?
DR. GOODMAN: Thank you, Dr. Samson. This is Dr. Ip.
DR. IP: It's not an unreasonable approach if there are really no data, but we will look at it as at the lowest rung of how we judge the quality.
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MR. SAMSON: Right. I would be concerned that even within these risk categories there could be quite a bit of heterogeneity that could explain some of the differences that were apparent.
DR. IP: I'm not an oncologist.
DR. GOODMAN: From a methodological standpoint, that is plausible.
MR. SAMSON: Right. One other point. Some of the treatments that -- and this is targeted at the Tufts people. Some of the treatments, the rationale is to focus the treatment on as highly localized a target as possible. And I wanted to just put out for some of the radiation oncologists, is there a possibility that by having such a highly localized treatment, there might be some disadvantage in terms of the long-term efficacy outcomes by maybe undertreating micrometastases just outside the prostate.
DR. GOODMAN: I see Dr. Grimm at the microphone. Are you addressing this question,

sir?
DR. GRIMM: I'm addressing the former statement he made about the variability of
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these groups. If you look at those, there's ranges in those low, intermediate and high risk groups, and I think that you can see there is a range in those groups. But that was the importance of that data, is that you could see the ranges there but they also cluster around a range and I think that's valuable, because we have no other data.
DR. GOODMAN: Thank you. So cluster or not, the number of studies is few. Okay. Did you get a response to your question?
MR. SAMSON: I actually didn't.
DR. GOODMAN: Did you want to direct that question to any one of the presenters?
MR. SAMSON: Just maybe Dr. Lee, if he's still here.
DR. GOODMAN: Dr. Lee. You may want to plant yourself closer to the mike, sir.
DR. LEE: A valid question. For the low risk population, if you actually look at the surgical pathologic series, the chance of having significant extracapsular extension, seminal or bladder involvement in those cases is exceedingly low. And you know, the reality is any of the treatments, including
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brachytherapy, CyberKnife, are treating the prostate with some small margin, it may not be a large margin. But we do understand that the problem of treating with too tight of a margin, it's not really the issue regarding microscopic disease, I think we select patients appropriately for that, but we're risking a marginal miss. In the Dutch series there's a subset of patients that were treated with IMRT and radiopaque markers through image guidance, but they're using margins of less than three millimeters or approximately three millimeters, and they actually saw higher PSA failure rates in those patients. So we're good, we just have to understand what the limits of the technology are.
DR. GOODMAN: Thank you, Dr. Lee. I have Doctors Schwartz, Jarvik and Steinbrook. We're getting to noon now. If these can be made brief we'll take them now, but if you prefer a little more laxity in time, we'll wait until after lunch. Dr. Schwartz, what would you like to do?
DR. SCHWARTZ: Very briefly, a

question for Dr. Zietman. Anthony, about the
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U.K.-Canada study, without asking for results, it's a question of the structure of the study, what was the follow-up of that study that results are going to be presented for, and what's the planned follow-up, what's the time course?
DR. ZIETMAN: Well, most of the information is embargoed so I can't really divulge it.
DR. SCHWARTZ: I don't want the results, just in terms of the --
DR. ZIETMAN: The median follow-up is six years, representing eight-year data.
DR. GOODMAN: Thank you. Dr. Jarvik.
DR. JARVIK: This is, again, just for Dr. Grimm, a clarification about the criteria that were used for your summary, which is quite different from the Tufts group TA, and you didn't require there to be a control group or a comparator to be included in your summary; is that correct? The reason a lot of studies were excluded from the Tufts group TA, it seemed that they were what they called single cohort studies, or with no adequate controls, and that wasn't one of your criteria, was it?
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DR. GRIMM: No, it was not. The expert panels which you saw were just 25 people, did not feel that was necessary. We were just trying to get a snapshot of what the current results and the current literature today are. We realized that the truth of that data is going to be somewhere in the middle of all those ranges that we showed and that, you know, you weren't going to get a cohort to compare.
DR. GOODMAN: Thank you, Dr. Grimm. Dr. Steinbrook, if it's brief, and then we'll get to Dr. Umscheid right after that if we can before lunch. Dr. Steinbrook.
DR. STEINBROOK: Some of the speakers did indicate that roughly speaking, a fifth of the patients will get watchful waiting, a fifth surgery, two-fifths radiotherapy, a fifth androgen deprivation therapy. Is there any data which is more specific within this black box, I hate to use that word, of radiation therapy? We've heard about many many different approaches to treatment. Do we have any sense as to whether some are more common than others on a population basis?
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DR. GOODMAN: Does any presenter have basically a distribution of therapies?
DR. STEINBROOK: Within radiation.
DR. GOODMAN: Yes, within radiation. Dr. Steinbrook, I see none, which in and of itself is not remarkable. Thank you, sir. But if someone does have a good answer to that following the lunch break, Dr. Steinbrook would be interested in seeing it.
Dr. Umscheid, last man before lunch.
DR. UMSCHEID: With the presentation today, I'm starting to feel more and more comfortable that at some level treatment for prostate cancer improves mortality, but a lot of the data that has been shown isn't risk stratified. And the only two studies that I've seen that showed that treatment for prostate canter improved mortality is the study on radical prostatectomy versus watchful waiting, and a study on hormones and, external beam radiation therapy versus hormones. So for those two studies what I wanted to know is what percentage of the population is low risk and what is the mean or median age of the patients in each of those studies? And I think

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Dr. Olsson could probably answer the radical prostatectomy question if he's still here.
DR. GOODMAN: He is. Dr. Olsson, would you like to respond to that? He's approaching the microphone now.
DR. UMSCHEID: And maybe Dr. Lee for the Widmark study.
DR. GOODMAN: Remind me, was the Widmark study part of the Tufts? It was not, just to remind us all. Dr. Olsson.
DR. OLSSON: I'm not a hundred percent sure what the age range population was in the Scandinavian study. I think it was, I would -- I want to say something up to 67 years old, something of that nature would be the high level, I think it was 55 to 67 or 68, and I don't know what it is in the radiation therapy group.
And you asked about risk. These were high risk patients. In other words, these were not patients who were PSA diagnoses, these were patients who either had nodules present or symptoms.
DR. GOODMAN: Thank you, Dr. Olsson. And I believe Dr. Lee was going to have the

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last response before the lunch break. Dr. Lee.
DR. LEE: For the Widmark study, since

they're not using Gleason score, they used WHO grade, it's hard to tease that information out. But I would say that the majority of the patients would be kind of considered more in the high risk category. As far as the median age, I think it was approximately around 68, but I do have the manuscript in my briefcase if you want to look at it.

DR. GOODMAN: Thank you, Dr. Lee. Thank you all from this morning, our presenters, scheduled and otherwise, and otherwise. Panel, I want, before we break, I want to remind you that we are going to address these specific questions about adequacy of evidence and what it says. I understand we talked about other kinds of therapy, but some of those types of therapy aren't directly germane to our questions. So do start thinking about at least the first two questions, about whether the evidence is adequate or not to draw any findings.

Please do look at your watches and other timepieces, add 60 minutes, and we will

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see you then. Thank you very much.

(Lunch recess.)

DR. GOODMAN: Welcome back, everyone. Before we broke for lunch, we had our questions to presenters. In addition to that we had some discussion among the panel. The agenda calls for what is described as an initial open panel discussion and we will have that discussion, but I would just say to the panel that if we think that we need to pose a specific question to one of our presenters, you can do that as well. So it's not necessary that we just have this conversation among ourselves.

And just to get something started here with our discussion, I'm going to ask the Tufts team -- the Tufts team needs to return to the front of the room, if you don't mind. I'm just kind of anticipating what our first question is going to be for our panel. I just remind us that it talks about the adequacy of the evidence to determine if radiation therapy for the treatment of localized prostate cancer affects a certain set of health outcomes? So radiation therapy, RT, and I recall your slide, I think it was 101, where it

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had across the top row, showed RT versus NT, radiation therapy versus no treatment. Given the evidence or lack of it that was presented this morning, is there any reason

why, given the paucity of evidence that you reported, that we need to subdivide question one by external radiation or brachytherapy, or any particular kind of radiation therapy. It seems, at least to my observation, to my eyes, that you had insufficient evidence across the board there, and that it's not likely there was sufficient evidence or good evidence for any particular form of radiation therapy. Is that correct, Dr. Ip?

DR. IP: That is correct.

DR. GOODMAN: Okay, thank you. Please don't take so long with your answer next time.

(Laughter.)

Thank you, sir, very much. Dr. Mock, on that point?

DR. MOCK: I wonder if now would be a good time, maybe after that response, for Dr. Ip to give us the answers to the question that was posed prior to the break on the studies.

DR. GOODMAN: Do you want to remind

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us, Dr. Mock, what that was?

DR. MCNEIL: Oh, actually he already showed me. The question was, what was the median follow-up? I asked the Tufts group, what was the median follow-up for most or all of the studies, and he showed me the answer.

DR. IP: We took a quick look at all the studies. We haven't finished counting, but we only have about 62 studies, we counted about 40 or 50 of them, and if you only want the studies that had ten or more years of follow-up, you have only about four or five studies.

DR. GOODMAN: Four out of five out of the 45 that you looked at, out of the 62 total, about ten percent.

DR. IP: Yes.

DR. GOODMAN: So four or five out of the 45 that you looked at during the lunch break, and of course 45 was the majority but not all of the 62 that you had captured.

DR. IP: Right.

DR. GOODMAN: Okay, thank you. Dr. Dvorak, on that?

DR. DVORAK: I think it's important to

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realize that with a median follow-up of ten years, you're now looking at patients that were treated in the early '90s in order to get to that length of follow-up, and I think it's important to realize that the technology back then versus the technology now may not be

comparable.
DR. GOODMAN: Thank you. Again, we've got the moving target issue. Dr. McNeil, what might you conclude from that preliminary finding?
DR. MCNEIL: Well, I might conclude, but I don't think anybody wants to hear it, that there's going to be a lot of ones in my responses.
DR. GOODMAN: Okay, thank you. You're kind of giving your answers early, aren't you?
DR. MCNEIL: I'm tipping my hand.
DR. GOODMAN: But we know that you're flexible in the face of good data.
DR. MCNEIL: I always listen to the data.
DR. GOODMAN: Thank you. And Dr. McNeil speaks for Dr. McNeil only at this moment and not for all the panel, in all

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seriousness.
I have another question starting with the Tufts team, and again for clarification looking down the road. Our questions two and three refer to comparisons of external beam radiation therapy versus watchful waiting, and in number three brachytherapy versus watchful waiting. And it seems from the discussion thus far today that the term watchful waiting may not be the best term of practice and art here. And furthermore, to the extent that we want to rely at least in part on the Tufts EPC study, you did not use as a comparative term watchful waiting, you used, I guess it was no treatment and/or active surveillance; is that correct?
DR. DVORAK: Or no initial treatment.
DR. GOODMAN: Or no initial treatment, okay. Is there a single encompassing term for what you did? And could you come to the microphone. What is the most concise way to describe what you used in that place?
DR. DVORAK: I think this is a difficult question, and the reason we used no treatment or no initial treatment is that the terminology may have evolved somewhat over the

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years, whereby historically as was presented earlier, watchful waiting would be that both the physician and patient committed to no radical treatment and you would only palliate symptoms as they developed for the disease. Whereas more recently, particularly in the United States, that approach has become more the active surveillance approach where you

monitor patients, and if there's felt to be a progression you treat them. And so I'm not sure that there is an encompassing term for this, which is why we ultimately settled on no treatment or no initial treatment as our comparator, and I think I would defer to perhaps some of the more senior radiation oncologists in the audience.

DR. GOODMAN: Right. We might go forward with them, but you have to keep in mind that we're dealing with the evidence that we have, and the evidence that we have was generated at some point in time, so we recognize that.

I'm just wondering, panel, it did seem that the term watchful waiting might even for our purposes be insufficient or inadequate, and

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if we might substitute the term watchful waiting with no treatment or no initial treatment. Does anybody object to that? It probably aligns well with the evidence as we've heard it today, and it's a little bit more current and applicable than the term watchful waiting. Does anybody have any comments on that? Dr. Fischer, and then Dr. Potters.

DR. FISCHER: The definition, I think this goes back to Parker's 2004 paper in Lancet Oncology, is that, the aim of watchful waiting seems to be palliation, and the active surveillance or whatever you want to call it is actually the outcome that is desired as cured. I wonder whether or not it is correct statistically to have the study in which you are comparing something which is palliative with something that is curative. I suppose people do it all the time, but it seems that in this particular disease, since we don't know which patients should be treated, it might be better to have active surveillance or something, or no initial, because as I understand it, watchful waiting means even if your PSA goes up to 476, nobody is going to do

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anything about it.

DR. GOODMAN: Dr. Potters, on that point?

DR. POTTERS: So, I think we should leave it based on the vernacular and terminology that was based on published literature. I think the idea of no initial treatment could also be flipped to delayed therapy, which could also be flipped to sort of active surveillance. And because that reflects

a more modern approach to patients that had very low risk disease and because as one of the presenters had outlined, that the protocol for that management is evolving and really not set, I think we should use the terminology that was in the literature. I think it creates ambiguity between a modern concept against, you know, older data.

DR. GOODMAN: Okay. But there was no single term used in the literature as I understand it, right?

DR. POTTERS: I would say that the term that was used, you know, I think everybody's paper probably said watchful waiting or WW, and that's sort of the way that

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it's put in the literature.

DR. GOODMAN: Dr. Steinbrook.

DR. STEINBROOK: I guess I would ask, and this may not be the thing that you can answer immediately, but of the studies which you considered okay to include in your analysis, what was the distribution of terms that they used which fell into the group of no treatment or no initial treatment? So if hypothetically the term watchful waiting was used in 55 out of 60, I'm making numbers up for the purpose of asking the question, I think it might be reasonable to go from that. If on the other hand you found ten different terms which were being used, it might not be as good to single out one.

DR. GOODMAN: I know that's kind of asking a question on the fly, Tufts EPC. Dr. Dvorak, do you want to go with that?

DR. DVORAK: I think we will look through the data and tell you what the answer is.

I would just make a comment that there were only three studies that compared radiation therapy to this watchful waiting, no treatment,

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in terms of overall survival. So the number is going to be somewhere between zero and three.

DR. GOODMAN: And just a reminder to all of us, no matter how we define it, there does not appear to be a lot of evidence, at least as we've heard thus far today, no matter how we define it. So it may be that we will have some all-encompassing term that may say watchful waiting or no initial treatment or active surveillance, we might just say we will take any comers for those.

Yes, Dr. Hevezi.

DR. HEVEZI: I was just wondering if we do that, would our answer change if we used watchful waiting versus active surveillance?
DR. GOODMAN: Well, it's a small number of studies. It's feasible that it might and if that's the case, we will ask for clarification at that time. I think the more important thing, while the voting is very useful to the Agency, at least as important as the voting are the succinct directed comments that accompany it.
Okay. Other questions from the panel? I've got one other I would like to do add.

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Yes, Dr. Umscheid.
DR. UMSCHEID: Just for question one, just for points of clarification. When I read localized prostate cancer I think low risk, and it's just to confirm it's T1 through T2 as the RTOG defined it.
And then the second question is for radiation therapy, I read that as being any therapy, whether it's external beam radiation, stereotactic body radiation, or brachytherapy.
DR. GOODMAN: To your latter point we just answered that, and yes, any form of radiation therapy. We found no reason to subdivide that item.
With regard to localized prostate cancer, it's T1 or T2, correct?
DR. DVORAK: Correct.
DR. GOODMAN: Do we need any other qualifiers for that? Dr. Potters, yes, sir.
DR. POTTERS: So, when I think of localized prostate cancer, I do think of clinically defined prostate cancer based on the T stage, so yes, I would think T1, T2, but within that subcategory you have low, intermediate and high risk patients. So that

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doesn't, you know, you have to look at the evidence of patients who have localized high risk disease in addition to patients who have localized low or intermediate risk disease. So that the risk is sort of a combination of factors outside of the T stage, it's the Gleason score, it's the PSA that get factored into defined risk, and that's outside of or on top of the term localized. So the first hurdle is it's localized, the second hurdle is what's the risk.
DR. UMSCHEID: So is it low risk or high risk or both?
DR. GOODMAN: Well, the question posed

here is localized prostate cancer, so we know it's T1 or T2 and we might just stop there, right? Okay.
And again, if stopping there doesn't quite explain that you want to state or understand about that, say so in a narrative fashion. We can make that point when the time comes.
So Dr. Umscheid, that answered your questions?
DR. UMSCHEID: Yes.

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DR. GOODMAN: Another question, and I know that Tufts EPC did address it before the lunch break but I want to make sure I understood it, and I apologize for my being slow on that. There were several references made to this Widmark study of 2009, I believe, and the Widmark study was not included in the Tufts review. And I wanted to make sure that we understood here yet again why that was not included. Can anybody offer a response to that? Dr. Dvorak.
DR. DVORAK: I think there are two reasons. The primary was that the comparison arm was between radiation plus hormonal therapy versus hormonal therapy alone, and so the fact that there was an active treatment there, hormonal therapy there, we excluded it.
The second reason, about 80 percent of the patients had T3 disease, which is locally advanced disease, and about 20 percent had T1 or T2 disease. And so while a subset of patients that are at consideration here did qualify for that trial and potentially ought to be managed according to the results, it was by no means all of them.

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DR. GOODMAN: Is it fair to presume that the published article did not do a subgroup analysis of T1 and T2?
DR. DVORAK: As I recall, they did not, but I would defer again.
DR. GOODMAN: You don't recall that it did?
DR. DVORAK: I don't recall that it did.
DR. GOODMAN: Yes, Dr. Raab.
DR. RAAB: Dr. Sandler in his presentation made explicit reference to that study, and I wonder if he could inform us how that study impacted his recommendation.
DR. GOODMAN: Thank you. Dr. Sandler, would you approach the mike? And again, we're

obviously most interested in the evidence that applies to the questions before the panel today, but we're interested in your perspective.
DR. SANDLER: So, the Widmark paper, which obviously I consider to be an important one, it tested whether radiation therapy improves survival, 80 percent T3, 20 percent T1 and T2. They did a forest plot, so they looked

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at the effect for benefit to radiation therapy as a function of T stage. And I'm not, I don't know if it's a formal statistical subset analysis, but the forest plot shows that the benefit was the same size for the T1 and T2 patients as for the T3 in favor of survival. Does that clarify that?
DR. GOODMAN: But you're not sure that there was a formal subgroup analysis of T1 and T2?
DR. SANDLER: I'm not a statistician so I don't know whether a forest plot can count as a formal subset analysis.
DR. GOODMAN: But was it broken out in a graph or a chart?
DR. SANDLER: It was.
DR. GOODMAN: And do you recall whether it was or was not a statistically significant difference?
DR. SANDLER: It was statistically significant.
DR. GOODMAN: Okay. Now the comparator was hormone therapy alone, correct?
DR. SANDLER: Hormone therapy alone.
DR. GOODMAN: Dr. Raab, does that help

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answer your question?
DR. RAAB: Yes, it does.
DR. GOODMAN: On this point, Dr. Lee?
DR. LEE: Yes, sir. Just to follow on Dr. Sandler, the effect size for T1 to T2, the mean absolute reduction was 16. For the T3 patients it was closer to ten.
DR. GOODMAN: 16 and ten what, what are these units?
DR. LEE: In terms of percentage reduction, absolute reduction in risk of dying. So the actual effect size for the T1-T2 patients was actually more significant than it was for the T3 patients in this particular study, and it was statistically significant.
DR. GOODMAN: And this subgroup analysis you're reporting to us anyway was statistically significant.

DR. LEE: Yes, sir.
DR. GOODMAN: Nevertheless, the comparison was not to any of watchful waiting or active surveillance or no treatment, it was to hormonal therapy?
DR. LEE: Yes. Presumably I feel that the investigators felt that a lot of these

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patients, if they had no therapy whatsoever, would have been ethically a little bit of a gray area.
DR. GOODMAN: Although active surveillance might have been okay.
DR. LEE: Potentially, but I think the reality is it would have just been delayed intervention.
DR. GOODMAN: Thank you for your comments. Dr. Raab.
DR. RAAB: Based on that and reading through the testimony, that study came up again and again, and I'm not quite certain -- I'm curious that the professional societies that have been represented, AUA, ACR, ASTRO, used that study in making their own recommendations of what therapies to use for prostate cancer.
DR. GOODMAN: Okay. Do keep in mind, we do need to answer our questions today.
DR. RAAB: I know, but the evidence, the studies themselves as well as professional society integration of those studies with their other experience is important and is the evidence that we're considering.
DR. GOODMAN: Dr. McNeil, did you have

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a point?
DR. MCNEIL: No, I disagree. Do I have it wrong? I thought that was radiation therapy plus hormonal therapy versus hormonal therapy alone.
DR. GOODMAN: That is correct.
DR. MCNEIL: So that's nowhere in this comparison list so it's irrelevant, interesting but irrelevant.
DR. RAAB: I'm curious whether it impacted the judgment of these professional societies with regard to these therapies.
DR. MCNEIL: True, but it doesn't help us.
DR. RAAB: And that judgment is what I'm curious about in weighing the evidence.
DR. GOODMAN: Okay. That's a very helpful discussion. We tend here to be a little more inclusive, we're going to err on the side of listening, as long as it doesn't go

past 4:30 of course. And so Dr. McNeil's point is very well taken, a comparison presented to us does not involve hormonal therapy for that question.
Dr. Dmochowski, on that point, or
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excuse me, Dr. Carignan.
DR. CARIGNAN: I actually had a different question.
DR. GOODMAN: Anything else on this point? Dr. Fischer.
DR. FISCHER: It might be that radiation therapy only works when there's a background of hormonal therapy, which is something we're not asking.
DR. GOODMAN: Dr. Umscheid, still on this matter.
DR. UMSCHEID: I just want to support the notion that this is important and direct evidence to answer our question. And I think, you know, we could either choose to take a dogmatic approach to evidence-based medicine and answer these questions or, you know, we could think about all the evidence that's out there. So I do think it's indirect evidence for some of the questions that are being asked here.
DR. GOODMAN: Indirect evidence is not as rigorous or valid as direct evidence, I would safely say that.
DR. UMSCHEID: I agree.
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DR. GOODMAN: And I at least have not heard thus far a causal linkage, or if you could give me an A versus B and a B versus C from which I could draw an inference about A versus C, I might entertain that, but I haven't heard that yet.
DR. UMSCHEID: I think the issue is if there's a therapy that's equal in both arms, then you could argue that that might be neutralizing the therapy that you're testing. Now you could also argue that there might be an interaction between therapies, which is a whole other thing, but I think it's relatively well accepted in epidemiology that you can make an indirect comparison, but it's less valid than a direct comparison.
DR. GOODMAN: Right. We can make those indirect comparisons, we don't like to do it if there's some better evidence. I think you're suggesting that the evidence is not overwhelming before us here today and as I said a moment ago, we'll be a little bit more

entertaining of this. Just to follow up on Dr. Raab's question, if there is someone -- we typically

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don't do this very often, but if there is someone here who is a presenter or otherwise that is affiliated, Dr. Raab, with any of those societies that you mentioned, who's been involved in evidence-based practice guideline formulation that can address that issue, we will take that briefly. Dr. Raab.

DR. RAAB: I want to thank you for that, and I wanted to just pull out the committee's own evidence review guidelines, which recognizes there are many situations where the evidence is going to be scanty or difficult to secure, and I think Alan Garber wrote this. He said the committee should explore many sources in assembling the body of evidence to be used in the deliberations. They may include peer-reviewed scientific literature, and it references specifically the recommendations of experts, societies and even unpublished data, although the quality does drop. But the committee should consider it.

DR. GOODMAN: Thank you. And I would point out at the same time, Dr. Raab, that while we're always interested in opinions and expert consensus and so forth, it isn't data.

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DR. RAAB: That's true.

DR. GOODMAN: Now, Dr. Lee, do you have an answer in response to this specific question?

DR. LEE: Well, for the A versus B versus C perhaps, if you actually look at the largest observational studies where they're just looking at people not getting definitive local therapy for prostate cancer, as we pointed out, up to 80 percent of those patients were actually being managed with hormone therapy at some point in their lifetime, and so to say that they're not getting any therapy is probably not absolutely correct, they're getting hormone therapy. So that's 80 percent out of, I think that study included the Medicare serial database, so that's tens of thousands of patients.

And so if we know that those are the results with hormone therapy in those cases, I think to Dr. Umscheid's point, perhaps if we could make the step from B to C which would be hormone therapy alone, plus or minus radiation therapy may be applicable.

DR. GOODMAN: It may be applicable.
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Does any panelist want to comment on just how applicable that might be? Dr. McNeil, are you at all persuaded?
DR. MCNEIL: No, I'm actually not. I do understand the theory of A versus B versus C, but I just don't see it here in this particular case, Craig. We've got, you know, 62 articles, and I'm not sure why I would suddenly introduce this indirect line of reasoning when we have 62, albeit thin, direct lines.
And in terms of the point of the society recommendations and the like, I still think we have enough data so we don't have to ask for great minds to pontificate about what they would or would not do.
DR. GOODMAN: Thank you. And from a less than great mind, I would submit that I think we've dealt with this issue. And Dr. Raab, I really appreciate you bringing it up and am glad we had it on the floor.
Are there any other questions or other sorts of inquiries from our MedCAC with regard to the evidence, particularly as it pertains to our being able to answer these questions
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shortly? Dr. Satya-Murti? Oh, I'm sorry, I think Dr. Carignan was next. I apologize, Dr. Satya-Murti.
DR. CARIGNAN: I just had a quick question going back to question one. As I read it the question is asking, is there adequate evidence to determine if radiation therapy for the treatment of localized prostate cancer affects each of the following health outcomes kind of in general. It's not saying it affects it favorably or unfavorably, it's not asking us to make a comparison to another treatment or no treatment. And I just want to be sure that we're all going to respond to that question in the same way, that this is a very open ended question, and it's, does the evidence show that there is an effect, whether we like it or don't like the effect, if there's any effect at all based on the evidence that was presented.
And to my view, if you look at the slides from the Tufts group, slide number 98, there's all kinds of effects going on in that slide in the different subgroups that they looked at. So is that how we want to answer that question or are we trying to answer it in
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a more specific way?
DR. GOODMAN: This is one of the typical types of questions that we have, and it's the adequacy question, not what is the impact actually. It's do you have enough to go on no matter where the going on takes you, so this is, is there enough evidence available and that you would consider adequate, not bottom line evidence, adequate upon which to make some finding. And then whatever that finding might be is typically addressed in a subsequent question. Thank you for raising that question. You are correct that there is no particular comparison being made here. Dr. Satya-Murti.
DR. SCHWARTZ: Can I just follow up on that question, Cliff, just for clarity? So, I guess for example, if radiation therapy were effective for reducing mortality, it might be increasing adverse events, and so I think that's the question that's being raised, but it's in different directions.
DR. GOODMAN: The direction -- I'm sorry. Dr. Schwartz, the direction here does not matter for question one.
DR. SCHWARTZ: That was the question.

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DR. GOODMAN: Thank you, sir, glad you asked the question.
DR. CARIGNAN: This is the difference between affect and effect. This isn't asking if it's effective, it's asking does it have an effect.
DR. GOODMAN: Absolutely correct. Thank you for the distinction. Dr. Satya-Murti.
DR. SATYA-MURTI: You already discussed the point of, is it evidence of any kind or is it adequate, does it rise to the level of evidence. But anyway, my question was about another paper in the New England Journal, 2008, I don't know which particular paper it was, was that the Sanda paper? You included that in your analysis. Did you come to a different conclusion than some of the other presenters?
DR. GOODMAN: Are you addressing that to the Tufts team?
DR. SATYA-MURTI: Yes.
DR. GOODMAN: This is Dr. Dvorak approaching the mike.
DR. DVORAK: So, we have included that

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study, and it's one of those four prospective cohorts and two retrospective cohorts for

comparison in slide number 65 in our presentation. And what the study did was, it was a large multi-institutional cohort where. they looked at multiple different treatment options, and we just took out the radiation components, the low dose brachytherapy and the external beam radiation therapy. And as far as that comparison goes, it was one of multiple comparisons that we had, and the p-value for that particular comparison was not reported in the text. The p-value was not reported for the specific comparison that we were looking for in terms of brachytherapy versus external beam radiation therapy.

DR. GOODMAN: Okay, thank you.

DR. SATYA-MURTI: Slide 64, did you say?

DR. DVORAK: 65.

DR. SATYA-MURTI: And 66, is that a further explanation of 64 then?

DR. DVORAK: So, slide 65 primarily looks at the quality of outcome metrics, and there is the EPIC scores and the UCLA scores,

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which are multiple questions you ask the patient in terms of outcomes. Slide 66 is the RTOG scale, which is more positional centric, so they are different outcomes in terms of toxicity measurements, which is why we split them up.

DR. SATYA-MURTI: But all three refer to the same study and same data.

DR. DVORAK: No. So, the slide 66 is two studies which used the RTOG scale as its outcome measure. Slide 65 is four prospective cohorts which used the quality of life metrics, so it was different studies using different metrics as an outcome.

DR. SATYA-MURTI: And the statement that the strength of evidence is insufficient applies to all of them then?

DR. DVORAK: Correct. It's the composite.

DR. SATYA-MURTI: Thank you.

DR. GOODMAN: Thank you. Any other questions at this point? Dr. Umscheid?

DR. UMSCHEID: This will be quick. For mortality, we're defining that as overall mortality, or prostate cancer-specific

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mortality?

DR. GOODMAN: I just see mortality here. Any comments on that on the part of the panel? Again, this is a situation where there

just isn't a lot there for either. Any comments? Dr. Schwartz.
DR. SCHWARTZ: No, I have another question.
DR. GOODMAN: Okay, Dr. Schwartz.
DR. SCHWARTZ: The wording of the question, you know, I would answer this differently if I were answering a question in the way it's written, how confident are you that there's adequate evidence. I might answer it a little bit different if it said given the evidence available, how confident are you that there's an effect. So you know, in one sense you're evaluating the adequacy of the evidence, and in another case it's the confidence based on the evidence that it does affect it, and those are not equivalent here. So I just want to make sure that what we're interested in and what CMS is interested in is more clearly written in the question.
DR. GOODMAN: Unless CMS states

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otherwise, I think we will take the question as posed. I frankly hadn't gone down that road to make that distinction.
DR. SCHWARTZ: I hadn't until, after careful thought, about two seconds ago.
DR. GOODMAN: And remember, this panel is not making clinical judgments, we're not doing practice guidelines, we're not going to go treat prostate disease when we walk out of here, at least most of us aren't. So, I don't see any revised comment from the Agency. Seeing none, Dr. Potters.
DR. POTTERS: Yeah. I think in terms of question one, I think we've sort of beaten it up a bit, but in terms of question two and three we --
DR. MCNEIL: Would you please elaborate how we've beaten it up?
DR. POTTERS: Well, the discussion may still remain open but I think the direct, the indirect, and the value of indirect evidence in terms of answering question one, affect versus effect, that's euphemistically what I'm referring to in terms of question one. In terms of question two and three, I

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do think that there's value to a discussion on indirect evidence. The case that I was making before was the crosswalk between, you know, radical prostatectomy, watchful waiting, and additional literature on radical prostatectomy with a biochemical surrogate, an equivalent

biochemical surrogate in the radiation literature, some of which was presented today by Dr. Merrick as a crosswalk. And then the impact that despite the hormones, that the Widmark paper showed in terms of the overall natural history of prostate cancer being affected by radiation.

So, I do think there's value to the indirect literature that needs to be taken into account and that to discount it, given the fact that if you look at the mean follow-up of the 60 studies relative to the question that was answered earlier suggesting that you need ten years or greater of follow-up in terms of looking and answering the mortality question, you know, we're just not going to have that answer. And that sort of presupposes, you know, the answers to these questions if we don't take into account some of the indirect

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evidence.

DR. GOODMAN: Thank you, Dr. Potters. I don't believe anyone said we're going to ignore indirect evidence, and we put on the floor an opportunity to have someone here put together a succinct clear case for that. I don't know that I heard a very strong case for it, but we're not going to ignore that. I will say, however, that we are talking about therapies here, we're talking about many thousands of Medicare beneficiaries who may stand to benefit or may stand to be harmed, and I think we're looking for some pretty good evidence here upon which to make some important, to help inform decision-makers such as patients, clinicians and sometimes even payers based on our best assessment of this evidence. And I think what we're hearing now is a well intentioned effort on the part of all of us to find whatever evidence there may be that's relevant here, and I think we're stretching a little bit on this discussion but we're going to allow that stretching to make sure we've uncovered things that are going to be relevant. We're doing our best to find out

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what's out there. Okay.

Any other comments or questions? You know, if not, I think we might go back to question one and try to address question one, if nobody wants to object to that, and we're going to take it as is. I know there's been a bit of discussion about affect and effect, but frankly the question was written correctly with

the word affect, with an A. Yes, Dr. Klein.
DR. KLEIN: I just want to be sure before answering this. Does this apply to all patients, so that even though, for example, the Tufts group did not risk stratify, if there's a subset, can you answer this based upon the presence of a specific subset in which you believe there may be adequate evidence?
DR. GOODMAN: I'll say this, Dr. Klein. Try to be inclusive here. If you, Dr. Klein, consider that there is something that you would deem adequate evidence about any particular subgroup and you're moved to give a grade accordingly, a rating accordingly, we would certainly welcome that.
DR. KLEIN: Thank you.
DR. GOODMAN: Okay. I don't see any

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other hands raised or points to be made here. And you know, again, before we launch into this rating activity, do remember that while the ratings are of interest and relevant, just as important if not more important are your opinions, your observations, and we'll have time for comments later on. I know that the Agency takes into account all of these in any of its further deliberations towards making any considerations about policy.
And so we're going to address question one now, and just a few reminders here. We've got our little Olympic style cards that go from one to five. One is low confidence, three is intermediate confidence, five is high confidence, so low confidence is one, high confidence is five.
And we understand --I will keep talking until Maria returns. I thought she was going to be on her way back. So do keep in mind that we will ask for some accompanying comments. We don't have hard and fast strict highly detailed criteria driven explanations of all the terms, but that's okay, and we will proceed pretty soon, as soon as Maria Ellis

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returns.
In addition to showing your card, notice that you have a score sheet in front of you, and we'll have those as a formal record as well.
(Discussion off the record between Dr. Goodman and staff.)
I know that CMS has a bit of a problem today with their computing system overall, I understand that.

The panel may want to be thinking ahead to question two, which is about adequacy of evidence as well and it's a different -- this is a particular kind of comparison.
DR. FISCHER: Here it says improvements.
DR. GOODMAN: Yes. Question two is going to be your confidence about the evidence being adequate. Again, this is the adequacy question, not what the answer is or the direction, but it's adequate to conclude that the use of EBRT in this case improves those health outcomes compared to not watchful waiting anymore, but we redefined that term. What is it again, Saty?

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DR. SATYA-MURTI: Watchful waiting, which includes PSA, biochemical evaluation and biopsies.
DR. GOODMAN: I think we said no treatment or active surveillance. So again, this is about not the direction or what the evidence says, but its adequacy. And so for number one, remember, there are going be three parts, mortality, functional outcomes and adverse events. And we discussed earlier that number one encompasses all these forms of radiation. Yes, Dr. Mock.
DR. MOCK: You just made a sentence that I think was intended to be clarifying, and I didn't quite catch it.
(Record read.)
DR. GOODMAN: Right, so it's divided into three parts, question one is, so for question one you will vote three times on adequacy.
MS. ELLIS: If you would, please hold up your cards until I record your score. Also, there is a score sheet in your packet, so please make sure you record your scores on that; that way I can double check and make sure

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I didn't make any mistakes, okay? Thank you.
DR. GOODMAN: And Ms. Ellis, just a reminder that not all of us are voting members. The chair does not vote, and you do take separate vote counts for the group as a whole and then without the industry rep; is that correct?
MS. ELLIS: That's correct.
DR. GOODMAN: Can we proceed?
MS. ELLIS: Yes.
DR. GOODMAN: Thank you. Question 1.a. How confident are you that there is

adequate evidence to determine if radiation therapy for the treatment of localized prostate cancer affects each of the following health outcomes? First, mortality. One is low confidence, five is high confidence.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you.
DR. GOODMAN: B, the same question about adequacy of evidence, but this time pertaining to functional outcomes. Adequacy of evidence, localized prostate cancer, functional outcomes, radiation therapy.

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(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you.
DR. GOODMAN: Same question, this time regarding adverse events, so adequacy of evidence for radiation therapy, localized prostate cancer, adverse events.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you.
DR. GOODMAN: All right then. Number two is, how confident are you that the evidence is adequate to conclude that the use of external beam radiation therapy, whatever type, external beam radiation therapy improves, so we are talking about direction now, improves each of the health outcomes listed below as compared to a therapeutic strategy of, and instead of watchful waiting, I believe we said no treatment or active surveillance, and watchful waiting could fall under that. This is for mortality now.
(The panel voted and votes were recorded by staff.)
DR. SCHWARTZ: Cliff, I don't have a

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problem with this one, but do we want to use improves for the next two also? Is that getting where we want to get, something to think about?
MS. ELLIS: Thank you.
DR. GOODMAN: The question is the same except this time functional outcomes, we're looking for resulting in better functional outcomes, Dr. Schwartz, if that helps you answer the question. And remember, this isn't just watchful waiting, it includes also active surveillance, which isn't necessarily benign activity. So this is, how confident are you that the evidence is adequate to conclude that

the use of external beam radiation therapy of whatever type improves functional outcomes compared to a strategy of no treatment or active surveillance?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you.
DR. GOODMAN: And part C of question two is now about adverse events. How confident are you that the evidence is adequate to conclude that the use of EBRT improves adverse

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events, as compared to a therapeutic strategy of no treatment or active surveillance?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you, I have them.
DR. GOODMAN: Thank you. Let's proceed to question three. I just want to remind everyone that we are going to have some discussion questions following these and some opportunity to comment on the evidence needs and so forth later on. Question three is another improvement question. This is, how confident are you that the evidence is adequate to conclude that the use of brachytherapy improves, in this case mortality, as compared to the therapeutic strategy of no treatment or active surveillance? This is about mortality now, it is about the direction of the evidence, mortality, brachytherapy.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Same question, and now the outcome of interest is functional outcomes. How confident are you that the evidence is

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adequate to conclude that the use of brachytherapy improves functional outcomes as compared to a therapeutic strategy of no treatment or active surveillance?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have your scores, thank you.
DR. GOODMAN: Now proceed to adverse events, this is 3.c. How confident are you that the evidence is adequate to conclude that the use of brachytherapy improves incidence of adverse events compared to a therapeutic strategy of no treatment or active surveillance, adverse events?
(The panel voted and votes were

recorded by staff.)
MS. ELLIS: I have your scores, thank you.
DR. GOODMAN: Thank you. Now we're going to proceed to question four, which involves three sets of comparisons, three sets of comparisons. And just to remind you, all three involve stereotactic body radiation therapy or SBRT, including CyberKnife therapy.

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And we're going to compare SBRT, first, to EBRT, external beam radiation therapy, that will be A. B will compare it to, compare SBRT to high dose rate brachytherapy, and the third comparison is going to be SBRT to, it should be low dose rate brachytherapy. So those three comparisons all of which involve SBRT, each of which will involve looking at three types of health outcomes.
And just to remind you again for question four -- well, actually, to remind you that back in question one when we were talking about adequacy of evidence, it did include the various forms of radiation therapy, including SBRT by the way, so that was encompassed with regard to adequacy, and now we're moving to particular sets of comparisons.
And so 4.a is going to be, how confident are you that the evidence is adequate to conclude that the use of each of these modalities below improves, improves each of the health outcomes listed for the identified comparator? In this case we're looking for evidence regarding the improvement in mortality of stereotactic body radiation compared to

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external beam radiation, so it's SBRT versus EBRT for mortality, what's the evidence telling you?
(The panel voted and votes were recorded by staff.)
Thank you. This is the same comparison except the outcome's different now, it's functional outcomes this time. And once again, it's stereotactic body radiation or SBRT versus external beam radiation for functional outcomes. And recall that SBRT was including CyberKnife and EBRT includes the 3-D conformal radiation therapy, the IMRT and the particle therapy. This is for functional outcomes now.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Thank you. Same

comparison, except this time the outcome of interest is adverse events, adverse events. SBRT versus EBRT, adverse events.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Now part B of question

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four regards SBRT versus high dose rate brachytherapy, otherwise know as HDR. So it's SBRT compared to high dose rate brachytherapy, and again, this is the conclusions you can draw about making improvements, this time mortality. SBRT versus HDR, high dose rate brachytherapy, for mortality.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them.
DR. GOODMAN: Thank you. Same comparison, the outcome of interest this time is functional outcomes, SBRT versus high dose rate brachytherapy for functional outcomes.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have your scores.
DR. GOODMAN: Thank you. The same comparison, this time for adverse events. SBRT versus high dose rate brachytherapy for adverse events.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have the scores.
DR. GOODMAN: Thanks. We will move

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now to the third comparison, this is part C of question four. This is SBRT compared to the low dose rate brachytherapy and remember, it's a different modality, SBRT compared to low dose rate brachytherapy, and the first outcome of interest is mortality.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have your scores.
DR. GOODMAN: Thank you. Part two of this question is SBRT versus low dose rate brachytherapy for the outcome of functional outcomes. Functional outcomes.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have your scores.
DR. GOODMAN: Thank you. And for the third and final part of part C of question four, it's SBRT versus low dose rate brachytherapy for adverse events.

(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have the scores.
DR. GOODMAN: Thank you. Now those have been our comparisons or head-to-head types
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of comparisons for the three main types of health outcomes of interest.
We're now going to proceed to question five, which is what they call external validity or generalizability. We're always mindful of the fact that CMS cares about all Americans but certainly for the Medicare program, the elderly or disabled, and sometimes available evidence, good or bad, does not always align with or account for the Medicare beneficiary population, so question 5.a is going to ask you about generalizability to the Medicare patient population. I recognize that we're asking you to kind of roll up all the kinds of observations and findings you made about questions one through four here, but please do your best on this, and again we're going to use our cards, where one is low confidence and five is high confidence.
How confident are you that these conclusions, those are the ones that you addressed in the four previous questions, how confident are you that these conclusions are generalizable to the Medicare patient population?
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DR. JARVIK: Can I just ask a clarifier?
DR. GOODMAN: Yes, Dr. Jarvik.
DR. JARVIK: If we thought that there wasn't strong evidence for the other questions, but we think that what evidence there is is generalizable to the Medicare population, do we vote that we have high confidence that it's generalizable even though the evidence is weak or nonexistent?
DR. GOODMAN: Good question, thank you for asking it. It isn't a question of whether it's good evidence or bad evidence. Regardless of how good the evidence was, you drew some conclusions, and would those conclusions extend to or apply to the Medicare beneficiaries, whether the evidence was good or bad. Whatever your conclusions were, you apply them to this beneficiary population.
So, how confident are you on a scale of one to five that these conclusions are generalizable to the Medicare patient

population?
(The panel voted and votes were recorded by staff.)

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MS. ELLIS: I have your scores.
DR. GOODMAN: Thank you. Question 5.b has to do with what we often call the distinction between efficacy and effectiveness, where efficacy is how good is the evidence for the ideal circumstance, and effectiveness is how well does it apply to community-based settings, routine care settings and so forth.
Dr. Satya-Murti, did you have a point?
DR. SATYA-MURTI: Yes. That's the tentative question, but because we're including proton beam which is not quite available yet, and SBRT, we are lumping them all together to the conventional conformal treatment, to the more advanced, technologically advanced. So we are considering looking at them all, and extending it to community centers and university centers.
DR. GOODMAN: Yes. Whatever the technology and however advanced it may be, are the findings that you derived to this point applicable to community-based settings? And I understand the distinction that Dr. Satya-Murti made with regard to the placement of some of these technologies.

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So, how confident are you that the conclusions for questions one through four apply to community-based settings?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have your scores.
DR. GOODMAN: Thank you very much.
So, if it pleases you, you can put away your cards now and we're going to move to some discussion questions that don't involve rating, but they do involve your considered expert judgment.
Let's move into question six. If one were to observe the set of scores that you just provided and if one were to have listened to the deliberations to that point, you might observe that the MedCAC doesn't consider that all of the evidence that would be desirable is available, so question six asks, what type of additional evidence on the impact of radiotherapy and prostate cancer outcomes is needed to improve decision-making in the approach to treating localized prostate cancer?
So question six is about basically the gap in

evidence, what gaps in evidence, to the extent
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that they may exist, what those are, what are those evidence gaps.
And then in question seven we'll talk a little bit about particular types of medical research that might be used to address those evidence gaps, basically what kinds of studies might we need to fill in those bits of evidence. And I recognize based on past experience that sometimes these questions overlap a little bit, that's okay.
And again, we'll take all the points in a moment. The value here of this discussion on top of the value of the discussion with regard to the ratings is that, one, it is our, we're obliged to provide some advice to the Agency about the kinds of evidence it might be seeking or expecting over the years. Just as important, we hope that stakeholders in this issue, patients, clinicians, other decision-makers, all kinds of groups might even be listening with regard to evidence expectations that based on your expert view might be appropriate. And so people that are innovating and designing new procedures and new technologies and what have you, might be
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thinking early and, as they say, often, about evidence expectations henceforth. So that's why this is a very valuable conversation that I hope we're going to have.
And just, I believe I saw hands up, we'll do that, but the first hand I saw was Dr. Carignan.
DR. CARIGNAN: Okay. I'll probably end up answering both in combination, because it's hard for me to keep them separate. But I think in terms of the additional evidence that's needed, I think all the therapies that we looked at today all have a place in the armamentarium for treating patients with prostate cancer. Clearly all of them have demonstrated some level of effectiveness, and each their own unique risk-benefit ratio.
But what's not clear is what that risk-benefit ratio would be in a given patient population, and is there a patient population that's better served by one form of treatment versus another. So for me, having studies that not only are comparative in nature amongst the therapies or to, you know, watchful waiting or some type of surveillance, but also to really
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try and define the patient population more specifically that maybe that given therapy is better for. It's probably not likely that all of them are good for all people, but more work should be done to identify much more carefully the cohort of patients in the study.
I think one of the things that would help with that that is more of a research issue in addition, is having more molecular or genetic type bases of looking at the cancers themselves and utilizing that in sort of a more personalized medicine approach, to define that maybe one of these therapies is better for a given tumor type than another, and using that as some of the criteria to look at how best to then recommend these therapies. Because as we heard from a number of the patients that spoke, they were presented with a number of decisions and largely left on their own to decide which one is right for them, without really a lot of information one way or another to guide them.
DR. GOODMAN: That's great. Thank you very much, Dr. Carignan. If the panel doesn't mind, maybe we'll just take these in order, and if you're not ready to make your point, we'll

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circle back to you, is that okay? I see agreement. Sorry, Doctors Umscheid and Raab, but you'll be very important when we get to you, I assure you. And Dr. Satya-Murti, we will circle back to you. Would you like to make your point now?
DR. SATYA-MURTI: Not for this particular question; for the next one I will.
DR. GOODMAN: Dr. Dmochowski.
DR. DMOCHOWSKI: I underscore what was just said, because I do think it's important that we don't, not every -- we have to understand the nail that we're using our hammer to hit, so I do think we do have to segregate the patient population in a way such that we understand who we're treating.
The other thing that strikes me, and really both questions do dovetail together very nicely, is generalizability. And that's something that whether a particular intervention that is achieved in a multicenter controlled randomized trial setting, can that same data be construed, or achieved rather, in a private practice setting in Stillwater, Oklahoma, for instance, as we've heard a lot

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about Oklahoma. It's very important. And I think one of the critical things that will help

us with generalizability is registry type data, understanding the experience in new technologies or even current technologies in the general population, so outside the randomized controlled setting.
So I would strongly push, and I think that this has certainly become consistent across several of the surgical subspecialties, for registry type data to be kept for these various interventions in the general practice setting, not in just the advanced academic centers.
DR. GOODMAN: And the registry data will be used to collect what kinds of outcome information?
DR. DMOCHOWSKI: Both efficacy and adverse events, because I think pertinent to what Dr. Schwartz so nicely put earlier, we need to better understand the other impact for CMS, which is management of adverse events, which in my world has a tremendous impact on the Medicare budget.
DR. GOODMAN: Great, thank you very

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much, Dr. Dmochowski, very good comments.
Dr. Fischer.
DR. FISCHER: You know, I have been sitting here listening to all sorts of studies for a disease which is extremely common, up to 80 percent of people ultimately get it, it's a huge public health problem, and I want to argue from a different disease which is also quite common and is a huge public health problem, but is light years ahead of where we are in prostate, and that's breast cancer.
About 40 years ago a particular individual started the NSABP, and --
DR. GOODMAN: Dr. Fischer, you will have to define that for us.
DR. FISCHER: National Surgical Adjuvant something or another, and we all call it NSABP, I haven't thought about what it means in about 20 years. And this is Dr. Bernie Fischer, he's no relationship, but he has done an enormous contribution. And right now I am editing the sixth edition of my textbook which is a standard surgical textbook and the breast chapters are coming in. And it's amazing what they have accomplished in 30 to 40 years, such

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as saying if you're a woman who is 70 years old and older, chemotherapy won't be effective, please don't take it.
I can't conceive of that happening

within this setting. First of all, you've got urologists and the radiation therapists at each other's throats. I don't know that from here, but I know that from around. And you don't even know which patients you should treat, and you've been at it for 40 years. So what I would argue for is a centralized, perhaps centrally funded effort with a disease which is common enough to really be valued in order to do this, because there are one hell of a lot of patients that are affected.

And I wonder, with that large group of patients and a central funding mechanism with appropriate oversight, input from all the relevant specialties that deal with it, very much as in the breast cancer situation, in a cooperative fashion, such that if anybody here has had the unfortunate experience of having breast cancer, you don't get treated with anything until there's a conference and you see all three people, and people get together and

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say this is the appropriate thing to do with this particular patient. And I would hope that with enough money and certainly listening to all the randomized or so-called trials, that unifying them, putting them together with the appropriate input, you would spend less and you would get more for your money.

You also would have enormous numbers of patients. You could have the appropriate segments of the patient population that should be treated one way or another in a randomized prospective fashion, and you would continue to have your answers. Once people bought in -- and it's been a long time. Bernie Fischer is now 93, and he started this a long time ago and it's still going, people have still bought in and kept it going.

I think this problem is big enough to warrant such an effort, and that's what I learned today, is that this is going nowhere, I don't think, with the current way that it's being done. You've got this group which is this coalition and that group which is that coalition, and you have industry, and you have various proponents, but nobody's thinking about

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the big picture. And I think with up to 80 percent of the males in this country ultimately going to have prostate cancer in some way, shape or form, it's about time people started thinking about the patients.

DR. GOODMAN: Thank you very much, Dr.

Fischer. I'm noticing that we're talking a little bit about the evidence gap and maybe the way of getting it, so if you feel more at ease with addressing both the evidence gap and study design that goes with it, that's fine if you want to proceed that way. Dr. Hevezi.

DR. HEVEZI: I would like to see whatever evidence we begin developing is some quality oversight on the new technologies or the technologies that we're going to be evaluating, because I think it's only fair that we can compare apples to apples and oranges to oranges, so that if I do a study in a university or a community setting, that the kind of quality care that the patient is getting from whatever treatment procedure we use is being followed.

DR. GOODMAN: Thank you, Dr. Hevezi. Dr. Jarvik.

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DR. JARVIK: Thank you, Dr. Goodman. So, I think that given the paucity of evidence that I think we generally agree upon, that any evidence that can be gathered will be useful. And while RCT evidence is in dire need, and I think ASTRO actually is to be commended in that I think they're going in the right direction and long-term rigorous RCT evidence in this country and elsewhere will be gathered, but we obviously can't wait for that necessarily. And there's other evidence that's valuable. If we had high quality observational studies, prospective cohorts and case control studies, that would be very useful data also to gather. You know, I think that further data on biomarkers with respect to tumor genetics especially would be useful to be able to identify early on who is likely to need treatments that are being contemplated and who won't benefit from them will be important. To jump a little bit to question seven and how to bridge this gap, I know that, or correct me if I'm wrong, that these questions are not up for a national coverage decision at this point, but coverage with evidence

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development is I think a powerful mechanism that can be used to incent people to enroll in registries and into trials. And having been involved in a number of randomized trials, I can attest that they are extraordinarily difficult to conduct, and any way that CMS can partner with NIH, for example, and industry in facilitating these, I think would be useful.

DR. GOODMAN: That's great, thank you very much, Dr. Jarvik. Point noted about coverage with evidence development, among others. Dr. Klein.

DR. KLEIN: I would like to reiterate much of what others have said. First of all, I think medicine continues to remain more a profession than a science, and I think what we really need to do is develop mechanisms by which we evaluate a course of diagnostics or procedure of therapeutics in the face of a lack of epidemiologically rigorous evidence, and I think that's among the most important areas in which we can proceed.

As others have said, there is a need for biomarker development, molecular genetic, yes, but also perhaps proteomic and even

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morphologic, potentially all of those means in combination. And while there's unquestionably a need for randomized controlled trials, there should be a push to include prospective biomarkers from the get-go in these trials in order to attempt to substratify patients and potentially find those patients in whom an intervention works versus those in whom it doesn't.

And then finally, one point that I don't think has been sufficiently emphasized. I think Dr. Lee did present an image of a radiograph of a patient with very severe metastatic prostate cancer. And I do think it's important to understand that this disease for those rare patients that we discover with localized prostate cancer, that for those in whom the disease metastasizes, this is a very serious event, and I think we need to try to capture the severity of advanced prostate cancer in these studies, so that we're quantifying or measuring a disease-associated morbidity rather than looking merely at the morbidity associated with therapy.

DR. GOODMAN: Thank you very much, Dr.

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Klein, and among others, your point is well taken about subgroup analyses and using the new science of genomics and others to really ferret out these important differences that will feed into the demand for personalized medicine, quite appropriate for this discussion. Dr. McNeil.

DR. MCNEIL: So, I would like to support Joe Fischer's position and argue against the position of some of the others.

And I would ask the question, would we believe today that progress in breast cancer would have been made in terms of lumpectomies, mastectomies, modified radical mastectomies, adjuvant therapy plus or minus, various kinds of hormonal therapy, age-based chemotherapy, think of all the various combinations of those therapies, on the basis of observational data? And I don't think any -- I certainly as a woman, being not affected by prostate cancer here, I would not believe that. So I think we really need to be just as critical about the amount of or kinds of data that we accept for prostate cancer, and I would say that when the effect sizes do not

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seem to be enormous, we have all sorts of discussions about whether or not the side effects are this versus that, when the cost distribution is enormous, and I do realize we're not talking about costs here, but we do know in fact that our insurance companies will be other than Medicare, and when the cost differences are at least a factor of three or fourfold. And when we don't have any predictive markers other than low, medium and high on the basis of Gleason and PSA values, that we can possibly believe that there won't be some unobservable factors in patients that will affect the results of treatment. So I would strongly say we're wasting our money if we try to treat prostate cancer different from breast cancer in the way that we collect data to look at treatment efficacy. So I would argue that Joe is absolutely right. The professional societies have to get together. We have to do an NASBP large study for prostate cancer, and not think we're going to get anywhere with what's very popular in terms of an observational data set.

DR. GOODMAN: So Dr. McNeil, you're

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saying back to those RCTs and the highest level of evidence.

DR. MCNEIL: I think if we don't do that for prostate cancer, we're going to be sitting here in five years and wondering why did we do what we did. I just don't think it's a rational approach. It's convenient, but we can't let convenience get in the way of proper treatment for a disease that's affecting a huge percentage of the male population. It wouldn't have worked in breast cancer, so I see no biological reason to think that it's going to

work in prostate cancer.
DR. GOODMAN: Thank you, Dr. McNeil.
Dr. Mock.
DR. MOCK: I think we're certainly on the cusp of a new age in this country in health care with the recent bill signing, and I think it provides us an opportunity to really focus on how we're going to get where it is we need to be. And I think if we ascribe to the theory that increased variability decreases efficiency, that decreased efficiency is going to lead only to increased waste of resources. Evidence-based medicine is a foundation we can

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stand upon. It's a foundation that will, even though it's supposed to take five to seven years to get out to the practicing clinicians, it will provide an opportunity for uniformity with proven outcomes that add quality of life to those that are afflicted with the disease. I feel that, what more do we need for evidence? Well, look at the evidence that we've evaluated today. We need a lot more evidence. We need to know exactly what the most effective therapy that's stratified with comorbidities, age and specific disease is that's going to provide the best outcomes with the lowest side effects at the most effective use of our financial resources. That's what we need for additional evidence, and I don't think that we can wait to decide how to do it best five to seven years from now. As our population ages, we need these decisions ASAP, and it needs to be based on a sound foundation of evidence-based decision-making as we move forward in the era of health care reform.
DR. GOODMAN: Thank you very much, Dr. Mock, for putting in the context of health care reform's broader purpose, we appreciate your

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comments. Dr. Potters.
DR. POTTERS: I would like to echo a lot of the comments that were made, and while I'm a proponent of randomized controlled studies, and Dr. Zietman outlined a number of studies that are either going to shortly be published or that are ongoing, there are differences with breast cancer. I mean, the reality of a shorter follow-up to get an answer on mastectomy based on a randomization of an attractive opportunity for women at the time that it was presented to them led to a lot of women signing up. And I think the option of, say, radical prostatectomy

or radiation or expectant management based on a randomization given all the cultural impacts that it has on the patients themselves makes it very difficult in the current environment to run that type of a trial. We could sit here and argue that all of the time.
I do agree with the concepts of -- and so while I don't discount it, I just want to emphasize the difficulties in trying to run those types of trials. And then you're dealing with a disease that has a much longer natural

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history, layered on top of technology changes that are occurring almost on a yearly basis or less.
The idea of the generalizability concept doubling back through a registry is something that's being explored and it's something that I would be a proponent of given the outcomes of efficacy, adverse events, and not just efficacy, adverse events and quality, I think Jim Hevezi entered quality, but also changes in practice and how practice changes within clinics, that can be identified with registries.
And then lastly, my comments are that sort of the elephant in the room is, you know, and I agree with the ideas of biomarkers. And you know, we don't have the HPV head and neck marker, you know, which is clearly changing head and neck cancer radically, but -- and so I would agree with translational efforts to try and identify markers, but we're also dealing with a disease that's evolved, and it's evolved because of screening and it's evolved because of perhaps early detection, and perhaps the detection of certain disease or certain

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patients that don't need to be treated.
So my old rationale, you know, was sort of the 20-20 rule. 20 percent of patients are going to die no matter what you do, 20 percent probably don't need to be treated, and then 60 percent are benefitted by treatment almost no matter what you do. But I think that that's evolved in the last ten or 15 years to maybe a 10-40 where ten percent of the patients are going to die no matter what you do, 40 percent of patients may not be treated.
And as we debated today, the definition of active surveillance and how that impacts on how one defines a baseline of comparison, and then you add onto surveillance the concept of delayed therapy or salvage

therapies. So that if you were to look at watchful waiting, you know, there's a lot of moving targets, and to focus the camera on any one particular component, say just external beam or just stereotactic, or just proton, with everything else changing is going to be difficult.

And so while, you know, I'll conclude by saying yes, I think that randomized trials

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asking very specific questions that will encourage enrollment should be encouraged. I think the idea of registries and translational is sort of the way to go.

DR. GOODMAN: Thank you, Dr. Potters. So Dr. Potters offers that there may be a portfolio of methods, including RCTs and perhaps registries as well, to capture all the kinds and types of effects and outcomes we may be looking for. You also emphasized what we called earlier the moving target problem, always a challenge. Thank you, Dr. Potters.

Dr. Samson.

MR. SAMSON: Okay. As a representative of an EPC very much like the Tufts folks, I approach this as a systematic reviewer, and so it's obvious that I would be very interested in the study design issues. And hearing what has been said already about randomized trials, I'd have to agree with most of what's said. I think that it's absolutely vital that we get these randomized trials funded and completed and cataloged. I also understand obstacles to enrolling into randomized trials, and those are

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sociocultural and, you know, the best we can do is just make the best arguments we can in favor of evidence-based evidence. It's a difficult process and it's hard to get the messages out to a broad enough audience to have an impact, but I do feel very strongly about randomized trials, and I know that the Minnesota EPC, they stand very firmly that only randomized trials will give us the answers we need.

I'm involved in a project right now that gets at this very issue with prostate cancer, should we be focusing purely on randomized trials or should we also look at observational studies. We're getting input from a lot of people, so I'm not going to come out too strongly. But if observational studies are to be done, registries or whatever, it's really critical that they be done at a high

level of quality, that the collection of patient data is done in a very rigorous way. As a systematic reviewer I've seen just tons of observational studies and they don't really give us very useful information. And so, you know, if the observational studies are going to be done, they just have to be done extremely

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well.

DR. GOODMAN: Thank you. So again, the portfolio is important, you're emphasizing the most rigorous types, and while you might allow for observational studies in certain instances, you're not looking for them to be weakly or poorly designed, you're looking for more sturdy design. Thank you, Dr. Samson. Dr. Schwartz.

DR. SCHWARTZ: Thank you, Cliff. You know, while I was confident that there was an effect in question one for most of the things, I had little if any confidence about what the level of that effect was, and virtually no confidence on the comparative effects. In fact if question four had been written for any comparison, I would have voted ones for all of them no matter what I was comparing. So we're talking about, you know, one technology, but it would have been the same no matter which technology I was looking to approach. And it seems to me we're really back to square one here. I mean, we need to quantify efficacy, we need to quantify effectiveness, we need to quantify particularly

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the benefit-harm tradeoff. You know, as has been noted, there's a limited effect size here, there's huge cost distributions, and in those sorts of settings adverse effects and side effects become more important, and you're talking about patient preferences and patient-reported outcomes here, and we're really at square one here, and it's really almost ridiculous that we're talking about such a common disease that affects so many people, and that for a significant number of people it is a serious problem, that we don't have this information after all the number of people that we've treated. I mean, if the U.K. and Canada can put together a quarter million people, the United States should have been able to do this a long time ago.

I think, though, you know, my wife always says that my tombstone will say he kept his options open. And I agree strongly with

what Barbara and Joe were saying about randomized trials, I'm not going to repeat that. But I also feel real strongly about the need for rigorous observational studies. We need a systematic effect here and the reason

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is, as people said, you know, we're dealing with extended time frames, so we're going to need to look at proxy or surrogate measures. There is a difference between breast cancer in this sense, and we were talking about it at lunch a bit. We're dealing with, you know, device-based, the equipment-based technologies, and they evolve. You develop a drug, the drug is fixed, you know. And for surgical procedures like lumpectomy, that basically is saying that here you have equipment and, as you know, the technologies improve, they're going to evolve, and so what you're testing today will not be the same as what exists in the time frame that we have to look at.

And we also here have a situation where there are multiple outcomes of interest, and, you know, the reason we haven't done a better job in part is because we haven't tried, but in part it's because this is hard. We don't talk about comparative effectiveness research, it's like motherhood and apple pie, but it's a lot harder to achieve than motherhood. You know, there are a lot of --

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you know, here we have timing issues. It's not just should you be treated but when should you be treated. We can't tell the difference between lethal and indolent disease, that's an essential component that we have to figure out so we know what to do.

And we need to learn how to handle crossovers. And I think it was Dr. Olsson in his written comments, he did a very nice job of noting that there are like 20 or 30 different major issues or effects that you have to take into account, age, state of health, life expectancy, risk tolerance and disease, you know, risk stratification. So if we don't start doing this, I think it's going to take a multipronged approach, I think we need to think about biomarkers because they're just better predictors, you know, I think about them as diagnostic tests, except better than what we have.

And we also need to think about incorporating electronic medical records. I

don't think they're the panacea people make them out to be, but this is clearly a disease where some of the subtleties of clinical

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presentation are going to be as Barbara noted, because of the biases that are inherent in this with the selection biases, we're going to have to tease it out. But it's also going to take a methodologic investment by the research community, by NIH and AHRQ and others, because we don't have the methods to be able to use observational data the way we're going to have to use it for this problem.

DR. GOODMAN: Thank you very much, Dr. Schwartz, you stated we're back at square one. Dr. Steinbrook.

DR. STEINBROOK: I agree fully with the comments just made and the comments earlier by Dr. Fischer and Dr. McNeil, so I don't want to repeat.

I think this is a situation where ideally every patient treated would have the opportunity to either enroll in a randomized trial or, if not in a randomized trial, an observational study or be part of a registry. I think that for certain types of information, how safe and standardized is simply the delivery of the technology, what are the functional outcomes, what are adverse events,

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with some uniform definitions, with some uniform data collection, that that could inform certain sets of questions.

There are other questions. Ideally you want to, to bring this back to the doctor-patient situation, patients making informed choices, you want to know of a tradeoff between how you're going to be doing in terms of your tumor in ten years and how you're going to be doing functionally, what adverse events you might have in a year or ten years, and trade those off, because the answer is not necessarily going to be the same for a hundred out of a hundred individuals, and that's what we need the RCTs for.

But I think that there's certain types of questions which we can get other information for. So given such a lack of evidence for such an important and common problem, I think it really behooves us to maximize the ability to get that as quickly as possible.

DR. GOODMAN: Great, thank you very much. So it's a matter of methods and timing. Thank you, Dr. Steinbrook. Next is

Dr. Umscheid.

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DR. UMSCHEID: I'm concerned that with time, even over the next couple of years with meaningful use becoming more important, of health IT, with patients getting more involved in their healthcare, more engaged, getting access to their medical records, I think PSA testing isn't going to stay flat, I think it's just going to continue to increase. And my concern is that we're going to be treating a lot of patients who have prostate cancer diagnosed by PSA, a lot of those patients who have indolent disease which would never kill them. So like the comment made before, I have a feeling that in the future we are just going to be treating more and more people who would never have died or maybe would never have even been symptomatic from their disease.

So I think one thing that I really would like to see is a randomized controlled trial in low risk individuals, and a randomized controlled trial of almost any type of RT versus active surveillance.

Now that gets to a couple other brief points that I want to bring up. One is this issue of getting people to engage in active

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surveillance. There was a comment that was made earlier that a lot of people are hesitant to do that, because they would rather do something versus nothing when they're given a diagnosis of cancer, so I think more research has to be done about how to help patients make that decision and how to communicate what active surveillance means.

And I think for that, another line of research has to be done, which is really defining active surveillance, and maybe that's less research and more consensus, but that issue has come up quite a bit in our discussions.

And let me see if there's anything else. The only --

DR. SCHWARTZ: If I could just interject one thing, I wouldn't blame the patient here. In the U.K., when the leadership there decided that there was a different approach, the percentage of people going for active surveillance, watchful waiting, you know, deferred treatment has increased some 60 to 70 to 80 percent over the course of about two or three years. So I think what patients

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are doing is responding to the uncertainty that exists within the provider community in how we frame the issue. I don't think they're acting irrationally given where we stand and how we communicate the issue.

DR. GOODMAN: That was Dr. Schwartz, for the record. Dr. Umscheid, could you finish?

DR. UMSCHEID: And I think Andy brings up a point that maybe we could just use research or findings from other countries like the U.K. and integrate them more into our practice in the States to help patients understand the decisions they have.

And lastly, the issue of screening in general and prognosis in general. A number of comments were made earlier about it's unclear who's going to die from this and who's not going to die from it, so a lot of people made comments about tumor markers or whether it's screening in the blood, but obviously screening and then prediction of who's going to actually die from the cancer are key areas.

DR. SCHWARTZ: You notice that was offered by the only person who's too young to

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be screened yet.

(Laughter.)

DR. GOODMAN: Thank you, Dr. Schwartz. If you could just cease for a moment, Dr. Schwartz, you and Dr. Umscheid can take that up later. Dr. Raab, sir.

DR. RAAB: Cliff, just one thing. I wanted to thank the Tufts center. If you haven't looked closely at it, on page three of their assessment, it's a nice commentary on future research and I thought it was a very succinct list of studies that needed to take place, and a real recognition that sometimes we have to be pragmatic and not expect RCTs, and they call in particular for a prospective cohort study to assess this issue of proper dose and mechanism in providing the radiation treatment, and I thought that was right on, and that one page is a perfect starting point for what studies might be done.

DR. GOODMAN: Thank you very much. And I know that in their slide presentation there was at least one slide that did talk about suggested studies. But you're right, Dr. Raab, that does break it up in greater detail,

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I thought that was helpful as well, glad that you're calling special attention of the Agency

to that. Dr. Satya-Murti.
DR. SATYA-MURTI: Towards the end we spoke about patients having to put up with the anxiety of the diagnosis. I have a suggestion. Because we don't know the biologic inherent variability and behavior of the disease, perhaps we could do a little change in nomenclature, like the cervical Pap smear people do. The earliest of these cancers after histologic diagnosis has been made need not be termed prostate cancer. I would like to see them -- someone mentioned adenosis this morning, or something of that nature like atypia. So this way the anxiety factor is lifted off the patient, and some of them would continue to be so, but this would then give an opportunity of having to, quote, live with cancer. And this might, when it is publicized and published appropriately, this would engender a greater amount of data as to what happens to these totally localized cancers, and in turn, cancer itself should then be lifted off. That's all I've got.

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DR. GOODMAN: Great, thank you very much.
For the panel now, are there any more comments about two things? One, a comment about an evidence gap, or a comment about the kind of study design needed to address that evidence gap, any further comments? We've certainly run the gamut on types.
Dr. Steinbrook, please.
DR. STEINBROOK: Well, it's sort of lurking in the back of my mind, not a large -- well, I shouldn't say that -- one of many many issues, but we really don't know for a fact, I think that watchful waiting versus active surveillance, active surveillance involves doing things, is an intervention in some ways, and I think that's something that, in the fullness of thinking about this, we have to take into account.
DR. GOODMAN: Yes, a point not to be forgotten, thank you, Dr. Steinbrook.
Dr. Fischer, on methods or gaps?
DR. FISCHER: You know, there are some things going on besides electronic medical records, although connected with it. There was

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a small research meeting a couple of weeks ago and Dan Roden, who is the chair of pharmacogenomics at Vanderbilt, gave a presentation about what they are doing at

Vanderbilt as far as genomics. And in September every single outpatient, which is 80,000, will have his or her genome as part of their permanent medical record, and what they're hoping to do is have a program where, let's say you want to put somebody on Coumadin and you say I'll order two milligrams of Coumadin. The computer will speak to you and say well, that's probably not correct, what these people need is four milligrams of Coumadin because of their genomics. I don't know how much work has been done in the genomics of prostate cancer, I don't know how many patterns there are. That, in addition to everything else that was mentioned by the panel, is to see whether or not there are certain patterns in getting at, is there a certain pattern to people who have to be treated, or a group of people who may not have to be treated. Clearly at least two different types exist. Just a thought.

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DR. GOODMAN: Thank you, Dr. Fischer. Other comments? Dr. Potters, and we'll try to be brief on these.

DR. POTTERS: We're addressing gaps, is that right?

DR. GOODMAN: Evidence gaps or methods to address them.

DR. POTTERS: So, the other sort of gap, which is not an evidence gap, but it's a comparative gap, is surgery, you have robotic and open, and then there are other modalities that are being looked at in the community. So you have cryotherapy, you have HIFU, you have all sorts of hot and cold laser types of therapies, and anything that anybody can come up with is going to be treating prostate cancer in the next couple of years. And so I think part of the discussion, as evidenced by the number of different technologies within radiation oncology, but outside of that there are a whole host of other things that have to be addressed as a gap.

DR. GOODMAN: Sure. You mentioned a term that others might not have heard, HIFU. Would you explain?

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DR. POTTERS: HIFU is high intensity frequency ultrasound, which is an ablative treatment focused in this area.

DR. GOODMAN: Thank you. Other comments on evidence gaps or methods? Just in partial response to

Dr. Potters, just recall that CMS recognizes that there is a whole panoply of ways to manage this disease, and the questions that we were given today reflect outside inquiries from various groups that wanted certain questions answered, so this is not meant to answer the whole gamut there.

A couple more items of business, including a participative one. We've heard from the Tufts EPC as one of the presentations, and I want to thank you gentlemen and thank your whole team, we've heard from them. We've heard from our scheduled public commenters. We have heard from our nonscheduled public commenters, of which I believe there were 15, we've had a lot of interaction among the panel and the people here today. We've done a little bit more than is often the case at these meetings, which is we've engaged a broader

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group of people in the discussion today, which I think is always a good sign.

I've got a couple more closing comments to make but before we do that, whether it is our EPC team or the scheduled public commenters, or frankly anybody else in the room today now, if you think we have missed a very important point or we have not heard from you a very important point, tell us now. Have we missed anything very important? I don't want to leave the room until we've satisfied that.

Glad to see Dr. Lee, and if you could be very brief about it, Dr. Lee, we would appreciate that.

DR. LEE: Regarding active surveillance, those studies are ongoing. In fact M.D. Anderson is conducting an active surveillance study. I will say that of the active surveillance studies that are currently ongoing, there have been reports by Larry Klotz from Canada suggesting approximately 25 to 40 percent of patients come off active surveillance in four years and get definitive local therapy.

The goal of active surveillance, I'm

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not saying it's the wrong thing to do, I am saying that those patients, you know, if you look at our slide regarding what the competing risks of death are in those patients, as that denominator gets longer, those patients are going to need to be taken care of one way or another.

DR. GOODMAN: Thank you, Dr. Lee. We

await the peer-reviewed studies that document that. I believe this is Dr. Medberry. Sir?
DR. MEDBERRY: I just wanted to mention that, I guess it's probably obvious to everyone, but we had several questions asking whether or not stereotactic body radiation therapy was an improvement over other forms of radiation and the answer I think was generally no, but that really isn't the question. The question is, is it as good, or are any of the forms of radiation better than any of the others, and I think that question really needs to be addressed.
DR. GOODMAN: Yeah. We would look forward to addressing that and other questions probably just as soon as we got some better evidence upon which to make that consideration,

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and we very much look forward to that, and I think we had some very good suggestions about the evidence gaps and how to address them today, and I think we all look forward to doing that. Was there a final comment, sir? Yes, thank you for approaching the microphone. Remind us of your name again, please.
MR. KINDER: Fred Kinder. I don't think we can wait five years for technology. As the dose, as you know, the dose increases, the cure rate increases. We can't wait for ten years. If the dose is delivered more precisely, we have that technology today.
DR. GOODMAN: Thank you, sir, we appreciate your comment and we understand the importance of the time frame. We hope that it would have been better had that evidence been ready already today, but I think for now we're encouraging the generation of that evidence in a systematic way.
A final comment here unless, does any panelist have any final comment? No. Okay. Just a final comment. Yes, Dr. Umscheid.
DR. UMSCHEID: Cliff, I have one final comment, just a point that, I think if there is

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an RCT showing that radiation therapy were better than watchful waiting in a low risk population, then you would need less rigorous designs to show that different modalities of radiation therapy that better targeted an organ were better than their older alternatives. So I think if you get some of those foundational studies, then you can rely on the technical aspects of some of the newer technologies and how those technologies better target tissues

and deliver higher doses to smaller areas, to make conclusions about those technologies.
DR. GOODMAN: Thank you, Dr. Umscheid, that's a great point. Dr. Schwartz.
DR. SCHWARTZ: I think the other thing that was mentioned earlier that I would just like to underscore is we've got to start working together more effectively on this. The cooperative groups are still organized in an old fashioned way, there's the radiation therapists over here and the surgeons over here, and this is a situation where you're going to need both of them working together, along with primary care physicians actually, because of the active surveillance type issues.

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There really needs to be a cross-disciplinary effort here that's really integrated from the beginning, and it shouldn't matter how you enter, but that you still get into this.
And we're going to have to, just to underscore what Robert was saying before about uniform definitions and standards and methods of measurement. So the other thing is in the research community, I was thinking about this when the Tufts people were talking this morning, there is virtually no incentive to a researcher to just repeat what somebody else has done, and yet there's a real scientific value in sometimes repeating the same type of study, and it's very hard to get funding nowadays in the environment as to, you know, do what's considered a repetitious or derivative study.
You know, the new NIH criteria even more now touts innovation, which is really good for advancing science in certain regards but when it comes to medical care, we, you know, you never want to trust in one study, and yet there's a lot of stuff in the system that works against repeating that, so I think we have to

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think a little more structurally there.
DR. GOODMAN: Good point. And certainly consistent with our last commenter, patients need to be managed now, we have to go with the best that we can, but that does not diminish the call for better evidence.
DR. SCHWARTZ: And they need to be part of that coalition too.
DR. GOODMAN: Absolutely, it can't be done without all these stakeholders.
A couple final comments. Just an observation that I think that what we have

heard today, I was going to say Exhibit A, we've heard today Exhibit P for why we need comparative effectiveness research. In looking, was there good evidence of head-to-head comparisons, no. Was there good evidence on patient outcomes rather than biomarkers, no, that was insufficient. In the absence of patient outcome data, is there evidence based on a good surrogate, probably not. Is there evidence covering clinically important time frames for the course of disease, not enough. Was there evidence on effectiveness in real world settings rather

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than efficacy, perhaps in some cases, generally not very strong. Was there evidence for the likely importance of patient subgroups, including the priority populations of importance, not much at all. Is there an apparent commitment for us now to generate this new evidence, we haven't seen much of it to date, but I think we heard some very good suggestions about what needs to be done there. Another point that needs to be made is that this not just a U.S. phenomenon, this is a global one, and the demand for better evidence of the types that were sought today is not just a need in the United States. We're seeing this globally, we're not the only ones that need to generate better evidence. The demand for the strong evidence is not going to diminish. All the stakeholders here in the room today and the Agency heard some very specific suggestions about what the evidence gaps are, what kinds of studies there are that need to be addressed here. Finally, we heard about a lot of what sounds like good evidence in the pipeline, it sounds like it's pretty good stuff. We await

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that in its peer-reviewed form and we kind of wish we had seen that earlier, it would have helped a lot more today, but that doesn't mean we're not looking forward to and welcoming that more rigorous evidence as it comes out.

Dr. Salive, back to you.

DR. SALIVE: Thank you, Dr. Goodman. I wanted to give some closing remarks from the CMS perspective. First, I want to thank the panel members again for all your service and really thoroughly reviewing this evidence and being very thoughtful in your comments and your voting. Particularly the comments just now, I think, on the evidence gaps are very helpful to

us as we think about this.
I want to thank all the speakers and I want to thank the public commenters, and publicly recognize the chair and vice chair for their work to pull this together. And also to thank the staff, especially Maria Ellis, Ellie Lund, Deirdre O'Connor, Joe Chen, who put together the meeting today.
Some immediate next steps I think for this are, we will post the score sheets, especially for those of you on the web, our

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apologies that we did not read out the scores, but they will be posted shortly on the website here. We post ultimately minutes and a transcript of the meeting as well.
As one of the previous speakers noted, we currently do not have a national coverage decision open for this topic, and we will look at the results and really have a lot of internal discussions here about the next steps for us. But I will say for myself that, you know, it does appear there's a lot of evidence gaps here, there's a real difficulty drawing conclusions from the evidence reviewed today reflected by the votes. I think that would create a difficulty with doing a national coverage decision in this area, frankly, and I do think it's really also a difficulty that would extend to even trying to use coverage with evidence development as sort of a Medicare level to push on this area. But I do appreciate that this is an important public health problem and that it does have a lot of important clinical questions and questions of treatment and effectiveness that need to be answered, and hopefully Medicare can push in

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that direction to get some of those studies going.
So again, thanks to everyone for the day.
DR. GOODMAN: The meeting is adjourned. Thank you.
(Whereupon, the meeting adjourned at 3:05 p.m.)