Decision Support Tools to Guide Cancer Control Planning for Prostate Cancer
Webinar Transcript
Moderator: James Hadley
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Coordinator: Welcome and thank you for standing by. And this time, all participants are in a listen-only mode. After the presentation, we will conduct a question and answer session. To ask a question at that time you press star then one on your touch-tone phone.

Today's conference is being recorded. If you have any objections you may disconnect at this time.

I would now like to introduce Mr. James Hadley. Sir, you may begin.

James Hadley: Thank you so much.

This is James Hadley from the Office of Advocacy Relations. And I am the Advocacy Program Manager. First of all, I want to apologize profusely for the delay. We are having technical difficulties beyond our control. And so we want to go forward with the presentation. We will put the slides on the CISNET website and you will be able to hear verbally what it is we are saying today. And we will have the slides on the CISNET Web site as soon as possible.

So we thank you for your indulgence, and we are going to just go forward, okay.

Welcome to today's webinar on tools to guide efforts to reduce prostate cancer death, developed by the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network. Simply known as CISNET - C-I-S-N-E-T.

CISNET is a consortium of investigators, who focus on modeling to improve our understanding of the impact of Cancer Control intervention.

For example, prevention, screening, and treatment on population trends and incidence and mortality.

NCI's CISNET models have been developed to explain recent disease trends that may also be used to project future trends to help determine optimal cancer control strategies, and to ultimately reduce and prevent prostate cancer deaths.

This webinar provides an opportunity for those in the fields of cancer control, advocacy, public policy, legislative affairs, and clinical science. (Lauri)?

Coordinator: Yes, sir.

James Hadley: There is a buzzing in the line.

Coordinator: I am watching which one it is coming from, sir.

James Hadley: Thank you.

Coordinator: Thank you.

It is coming from (Ruth)'s line.

James Hadley: (Ruth), can you put your phone on mute please?

Woman: (Unintelligible).

Man: I can actually see who is connected.

Man: I just got in guys, for what it is worth.

Woman: Yes, it is working for me too.

James Hadley: Put your phone on mute, (Ruth), until we get to your presentation. Can you do that?

(Ruth Etzioni): I am trying to.

James Hadley: Okay.

(Ruth Etzioni): Hello?

James Hadley: Hello.

(Ruth Etzioni): Okay. Is that better?

James Hadley: Okay. We will try it again.

(Ruth Etzioni): Thank you.

James Hadley: This webinar provides an opportunity for those in the fields of cancer control, advocacy, public policy, legislative affairs, and clinical science, to learn how these decision support tools and models can address pressing policy issues, and guide the implementation of cancer control interventions to ultimately balance, benefits, and, cause.

If you would like more affirmation about CISNET, you can go to the CISNET web site which is CISNET - C-I-S-N-E-T .cancer.gov.

Today we have with us Dr. Eric J. Feuer - better known simply as Rocky. He is the CISNET Program Director, and chief of the Statistical Research and Applications Branch at NCI's Division of Cancer Control and Population Sciences. He will give an overview of the CISNET consortium.

We also have with us Dr. (Ruth Etzioni). I am going to apologize in advance for screwing up everybody's name. Dr. (Ruth Etzioni) who works in translation and outcomes research Fred Hutchinson Cancer Center in Seattle, Washington. She will talk specifically about the CISNET prostate cancer program and potential policy applications.

Dr. David Penson is the associate professor at the Department of Urology and Preventive Medicine at the University of Southern California. He will discuss the relevance of utilizing the prostate CISNET models from a clinician's point of view.

We also have with us as resource - resources during the question and answer period, Dr. (Alex Tsodikov).

(Alex Tsodikov): (Unintelligible).

James Hadley: (Tsodikov). Thank you.

And he is from the Department of Biostatistics at the University of Michigan.

And Dr. (Gerrit Draisma) from the Department of Public Health at (Erasmus) Medical Center in the Netherlands.

A question and answer session for participants will follow the panelist comments. So please grab pencils now. I know you already have them. You have been waiting to ask your questions. An operator will assist us when we get to that part of the program.

If you have friends or colleagues who could not join us live today, they can check in at the CISNET Cancer.gov website at a later date, and we will have the slides and the oral presentation that we are doing today.

So a few reminders before it's started.

I want to remind you that we have an understanding NCI toll-free teleconference series. And it is sponsored by our office, the Office of Advocacy Relations. And it provides an opportunity for the cancer advocacy community to learn more about NCI’s important cancer research programs and how advocates are involved.

Our spring series continues next week - next week on Wednesday, May 21st, from 2 to 3, with the topic Understanding the Role of NCI's Clinical Trials Advisory Committee.

Joining us will be Dr. Sheila Prindiville, who is the director of NCI's Coordinating Center for Clinical Trials. And that will be a simple teleconference - not a webinar. So that should be a piece of cake.

The final topic in the series will be addressing the complexities of cancer health disparities - NCI Center to Reduce Cancer Health Disparities. And it will feature the director of the center, Dr. Sonya Springfield.

So again, if you want more information on the Understanding NCI toll free Teleconference Series, visit our website - advocacy.cancer.gov. If you would like to find out about other teleconference topics, you can - or if you have questions or comments, you can send them to NCIadvocacy@mail.NIH.gov. Again, NCIadvocacy@mail.NIH.gov. I got that right.

Now, to begin today's teleconference, Dr. Rocky.

Eric J. Feuer: And I think I am in, so I think I can control the slides, (Lauri). Is that okay?

Coordinator: Yes, sir. You guys have control.

Eric J. Feuer: Well, welcome everybody. And I do apologize for the technical difficulties, but I think maybe we are on track now.

And I hope everybody is seeing a slide that says - that has the CISNET logo and my name in the front. And I am just going to give a very brief overview of the Cancer Intervention Surveillance Modeling Network.

So first of all, what is CISNET? I think James gave a brief introduction. It is the NCI sponsored consortium of modelers. And it's - we are focused on modeling the impact of cancer control intervention. That means screening, treatment, and primary prevention on current and future trends.

This is really the why questions in the analysis of cancer trends.

And then a very related topic that might be called optimal cancer control planning. We have modelers in four cancer sites - breast, prostate, colorectal and lung cancer. We already held a webinar a few weeks ago on colorectal cancer. That webinar is available to you on our CISNET web site. You can see the website at the bottom - CISNET.cancer.gov.

Well, what is unique about CISNET, in terms of modeling? First of all, we develop flexible models, which can handle the full range - what we call the full range of inputs - the different types of cancer control intervention.

So it can - in terms of puts, there could be the changing risk factor profile of the nation, different screening behavior, diffusion of new treatments and then other types of input.

These inputs all go into our different cancer models that the different investigators around the country develop. And outcomes, incidents, mortality,

other things such as costs and different things come out, depending upon model.

So these are really flexible models that can handle all the different types of inputs you might imagine.

Well, one problem with modeling is - one thing we want to do in CISNET is make the results of modeling more transparent.

And modeling has been marred in the past by somewhat of a lack of comparability of inputs, outputs, and basic definitions. And then a difficulty of understanding, comparing the different model assumptions and structure.

An example - this is not from CISNET, but an example that makes this very graphic is the result of four independent published studies of the cost effectiveness of spiral CT screening.

And you can see these different studies which occurred from 2001 to 2003. And the results are all over the place. From $2500 for quality adjusted life year saved all the way to $154,000 for quality of life - adjusted life year saved.

And when you try in a systematic way to review these studies and think about what are the differences, so you can better understand why they would get such different numbers, it is very confusing. Because there are differences in the target population, screening frequency, stage shift, assumptions about lead time and over diagnosis, sensitivity. So it really is a very difficult thing to make any sense out of.

So in CISNET, we have had several attempts to make modeling more transparent.

First of all, we use a comparative modeling approach. Sometimes we call these base case questions.

These are central questions to be addressed are all the groups with a common sense of set of inputs and outputs. So you could reduce the number of things that are changing at the same time.

Second of all, we have something called a model profiler. And that is a common set of web-based templates to enter model assumptions and structure. And this is available on our CISNET, website - our public website.

And occasionally what we do with within CISNET is have talks based on the model profiler, comparing a certain aspect of model structure. For example, how do the models implement post diagnosis survival?

And CISNET has been applauded by (ISPOR), at the International Society for Pharmacoeconomics and Outcomes Research - a taskforce that I support formed on good modeling practices for setting up a forum to compare model results and articulate reasons for discrepancy.

CISNET is just not in one model, but a group of models. And we work to compare and contrast the results of the model - models, giving more credibility to the modeling process.

Now, an example of a base case is the work by the CISNET Breast Cancer Group. And this is probably our most well-known results to determine the contributions of mammography and adjuvant therapies to the unprecedented 24% decline in breast cancer mortality from 1990 to 2000.

And this work by seven groups indirectly overturned some growing concerns that many of the randomized trials of mammography, which showed a benefit were flawed, because the consensus among the consortium was that it would be difficult to explain this large decline in U.S. mortality without a substantial contribution from mammography.

And this was published in The New England Journal of Medicine. There was an editorial - a follow-up in the New York Times that said, was seems most important is that each team found at least some benefit from mammograms.

The likelihood that they are beneficial today - beneficial seems a lot more solid today than it did four years ago. Although, the size of the benefit remains in dispute, indicating the - and this sort of indicates the power of comparative modeling.

I just want to make one final note about what it is like to work with CISNET investigators. So (unintelligible) CISNET investigators really invite collaborations on applying their model. It is a true collaboration. You would work together to decide inputs, model runs, and interpret results.

You are welcome to contact investigators directly. All of their emails are available on the website. Or you can send an e-mail to me and I can help provide guidance about which models might be best for your needs.

And there is some financial support usually needed to support running these models. But these costs are fairly moderate because we've already built the infrastructure. In other words, the National Cancer incented has provided the support to build these models and applying them and running them in a particular application is much more moderate.

So now, I think that gives you an overview of CISNET. I want to next turn things over to (Ruth Etzioni), one of our principal investigators from Fred Hutchinson. And she will review what the prostate group is doing in CISNET.

(Ruth Etzioni): Thanks, Rocky.

I hope everyone is now able to see my slides. I am, which was not the case a half hour ago. So I will be controlling the slides. And I am speaking as a representative of the CISNET prostate group, which consists of three separate groups of modelers, principal investigators and myself - (Alex Tsodikov) and (Harry De Koning). We are all on the line and available for questions after the presentation portion of the webinar.

Now people talk about not being able to see the forest for the trees. Today, we are talking about the forest and the trees. Rocky has ably given us the big picture of surveillance research - the forest. And in my presentation, I am going to focus somewhat on the trees and provide some details of the components of the models we use for surveillance research and how these might be turned towards the goal of developing sound intervention policies.

So what my primary aim in these comments is to build a bridge from surveillance research to policy development, where surveillance research involves linking interventions as they occur in the population, with populations in these trends.

And policy is the optimization of interventions to obtain target levels of cost and benefit in the population.

And the Bridge consists of the disease models that we have developed for our surveillance goals.

We believe that these models, once developed and calibrated in the surveillance setting can provide a valuable tool also in the policy-setting.

And of course today, we are talking about prostate cancer trends - prostate cancer. So let's begin by reviewing patterns of prostate cancer incidence and mortality in the U.S.

The left plot here shows incidents - (unintelligible) or incidents for blacks and whites - the bottom on mortality. And the curves clearly show a dramatic increase in incidence around the time when PSA - early 1980's - I'm sorry, 1980's, early 1990's when PSA began disseminating in the U.S. population - incidents more than doubled.

And prior to the advent of PSA screening, the lifetime probability of a prostate cancer diagnosis was about 9%. And it is now upwards of 17%.

Mortality, on the other hand has shown a decline (unintelligible) from 1991 to 2005, up more than 35%. On the right panel, you can see this mortality decline in the context of mortality trends in other cancers.

The purple curve here in - on the right hand side is the prostate cancer mortality curve.

Now the prostate cancer mortality decline began in 1992, just a couple of years after PSA started to become widely used in the population. So naturally, the question that everyone has been asking is whether these declines are a result of PSA screening?

An affirmative link between PSA screening and death rates declines would be tremendously useful information, because as yet, we do not have completed evidence, providing the efficacy of please so advise screening from randomized screening trials.

These screening trials are being conducted in the U.S. and Europe, but the test is already in the population. So we have had a cart before the horse situation, where an unproven technology has become widely used.

This is also being referred to as a natural experiment. But it is a highly uncontrolled one. And in fact, other important changes in prostate cancer management have occurred concurrently with the spread of PSA screening.

This slide shows PSA screening frequencies. This is a reconstruction from National Health Interview Survey and Medicare claims data, showing the dramatic increase in PSA screening in the early 1990's.

But in the '80s and '90s, there were a lot of changes in treatment. So the top right hand panel here shows the solid line decline in watchful waiting, and increases - the dotted curve in surgery during the mid-to-late 1980's. And the bottom display shows increases in (adjuvant) hormonal therapy used with radiation therapy in the early-to-mid-1990s.

Both radiation - both radical prostatectomy and (adjuvant) hormonal therapies used with radiation have been shown to be efficacious in randomized treatment trials.

So, how can we possibly decompose the mortality declines in the population into the portion due to screening versus treatment, versus potentially other interventions?

The central promise of CISNET is that modeling provides the way. And basically, all CISNET groups work by developing a model of disease progression, or natural history, which generates outcomes such as in incidence, mortality, and stage distribution at diagnosis.

Population screening and treatment patterns are then superimposed on this model. And their interaction with the underlying model produces a projection of outcomes with the intervention, which can then be compared with the outcomes without the intervention to produce an estimate of projection of the mortality decline, solely do to that intervention.

These graphics show projections from two CISNET models of prostate cancer mortality in the absence top panel and in the presence of screening together with observed mortality rates from here. We will return to these models later.

I just want to note that our models are also considering treatment, and produced projections with and without the treatment changes and I showed in the previous slide - the surgery and (adjuvant) hormonal therapy changes. So we are considering both screening and treatments.

Now, so far I have been somewhat vague about disease progression and the reason is, there are many ways to model it. And this slide now shows just in a quick snapshot of the disease progression models presumed in each of the three CISNET prostate models.

The progression models all have in common that disease progresses or proceeds through states, just - and the states in the Michigan Model consists of healthy, latent asymptomatic, and symptomatic disease.

In the MISCAN model, the states are defined by combination of stage and grade. So many more transitions between states are possible.

And the Fred Hutchinson model, actually models PSA growth over time. Disease onset occurs - the risk of the disease onset increases with age but then transitions from the localized to a metastatic state, or from a latent to a clinical state. The risk of those transitions depends on the current PSA level.

Both of Fred Hutchinson and the Michigan models include a grade designation, just - that I have just not included in these snapshots here. So all the models also consider grade.

Now, many of the events in the disease progression pathway are of course unobservable. But they produce observable end points.

So, we estimate - all the models estimate the unobservable progression rates by how well they generate the observable outcomes.

Formally, each model implements a form of maximum likelihood estimation that defines the underlying latent disease progression rates, yielding diagnosis frequencies that are close to those observed.

Thus, all the models are calibrated to the observed age and stage-specific incident trends in the population. Even though the underlying description of natural history goes beneath the surface to describe progression between latent disease progression events.

This - once the natural history model has been conceptualized and estimated, the intervention interrupt progression in that way, change outcomes.

This slide shows how - sorry, my animation on this side isn't working. The idea of this slide, for example, shows a natural history concept - shows a natural history concept of the Fred Hutchinson model. And I am going to proceed. Here we go. I am going to proceed - I was going to proceed to the next slide, but this slide is simply showing that, with screening the date of

diagnosis is advanced. And the day of death is shifted, based on the stage - the new stage of diagnosis.

And the result is a decline in prostate cancer mortality in the presence of screening.

And here we return to the results about mortality with and without screening under the two models that I showed previously.

Both models project that mortality would have increased in the absence of screening. In fact, the no screening curve also (unintelligible) specific survival in pre PSA era levels. So the no PSA curves may also be thought of as reflecting no treatment changes during this time.

The curves labeled PSA are the models projection of mortality given PSA screening patterns, and the resulting shift in stage from distant to localized or regional diagnosis.

As you can see, the projected mortality and the screenings does not match observed. The first model projects on screening accounts for about 70% of the difference between the top and bottom curve. And the second model about 45%. Thus, both models suggest a role for other interventions, like treatment changes in the mortality decline.

The models can also be - can also be used to quantify the cost of screening, like the over diagnosis frequency. This slide shows observed and projected incidents in the population for all three models.

The projected incidence is shaded and partitioned into screened, versus clinically detected cancers. The slide shows how the models - all the models calibrate to the U.S. population incidents - incident and presents the models estimates of over diagnosis and lead times.

Thus, in addition to providing answers to key surveillance questions, the CISNET work has provided us with three models of prostate cancer progression that have essentially been validated against the population experience.

How can these models be used for policy development? Very naturally. Rather than implementing a model of intervention as it occurs in the population, once you consider a host of proposed or candidate interventions or policies, apply these to the progression models, and compare the outcomes under the different policies.

And here I have an extended list of outcomes. And the list of outcomes that might be considered could even be more extensive.

Now, there are many different policy questions that the models could be used to answer. As an example, a particularly pressing one in prostate cancer screening policy is the issue of the PSA threshold for referral to biopsy.

In comparing, for example, a PSA cut off of 4 nanograms per milliliter, which is - has traditionally been the standard, versus a lower cut off, which has been proposed more recently.

The consideration of the policy implications of these different cut offs could be done directly via the Fred Hutch model, because this model directly links PSA growth with disease progression. But it could also be done via the (MISCAN) and the University of Michigan Models indirectly via of the effect of the alternative a threshold on sensitivity and specificity.

This slide just gives an - just lists a few of the candidate policies we want to consider. We talked about the threshold of comparison. There are many different policies that one could consider with the continuous screenings marker, relating to the values of the cut offs. Also the intervals for screening, the ages for screening.

But the models also consider different treatment options. And therefore, could conceivably model different treatment policies.

And even policies combining different screening and treatment criteria. And it will be important to consider these together. Because the more liberal screening policy will necessitate a more conservative treatment policy to avoid over treatment and vice versa.

So the models enable consideration of screening policies, treatment policies, and also of combinations.

I would like to end with a vision for how these models might be used in practice.

And our idea is to have a user interface. A very hands-on approach. We would not run the models. They would be a user interface to which the policy makers

could interact with the models to specify a host of input, candidate policies and desired outcomes.

And interface would then run the model. This would not only allow policy makers to quantitatively compare the benefits of the proposed policy, but this quantitative comparison would harness the full power of CISNET by basing results on population calibrated models. And also by having the ability to query multiple models.

So surveillance - in order to do surveillance, we would have to develop these models - these models can now be applied. And we are enthusiastic about applying them to policy issues through an interface of this sort. Working together with policy groups so that we can accommodate the outcomes of interest, and deal with the inputs of interest in a unified fashion, based on the technology that has been developed by CISNET.

I am now going to turn the floor over to Dr. David Penson who is a urologist working closely with us as we develop our models. And he will talk about the clinical potential for application of these models. Thank you.

David Penson: Thanks, (Ruth). I will see if I can take over the slides here.

I have been really lucky to be involved in CISNET. I am grateful for (Ruth) for including me.

I am not a biostatistician like the other investigators. I'm - as I often joke - just a dumb urologist who occasionally adds his two cents.

But I am excited to be a part of the CISNET group. Because I think that these models, not only inform policy. I think that really is the primary - the primary use of goal is to inform policy. But I think it could be also be very helpful at the bedside, at least to give patients additional information for them to sort of think through these difficult issues.

When we considered what - and I am hoping my slides are moving ahead here. When we consider the state of prostate cancer in 2008, we still have lots of questions but very few answers.

And (Ruth) alluded to some of these. I think patients deal with this everyday. The wonder does prostate cancer screening help more people than it hurts? And as Dr. (Etzioni) said, the cart has gotten before the horse. But I still think there are still some people out there who wonder, and even some patients whether or not this is a good thing.

Patients who are diagnosed with prostate cancer are told that many of their cancers are clinically indolent. Well, it begs the question, which cancers are clinically indolent and can be watched with active surveillance?

And finally, if patients feel they need treatment, they are left with a host of therapies, which they don't know the best choice for. And are faced with the question, which patients need aggressive intervention? And realistically, what kind of outcomes can a patient expect with a given intervention?

I think these - all these questions can be at least somewhat informed with information from the models from the various CISNET investigators.

When we think about prostate cancer screening and that first question. I don't want to spend a lot of time on this slide just to point out there are some real advantages and disadvantages.

Patients realize that it is easily easy. It is simple. All it is a blood test and a digital rectal exam. They know that early disease is curable and advanced disease is not curable.

But there are some disadvantages too, which I think sometimes are lost to the patient - but not always. That the value of screening isn't proven. The test characteristics of PSA screening are questionable, as (Ruth) alluded to. We don't even know the best threshold.

And let me tell you, I see a lot of patients who come in with a long list of their PSAs for the last 5 years/10 years and have PSA anxiety just following these numbers. And I am not sure we are helping them.

And finally, as I mentioned before, not all prostate cancers are clinically significant. And this makes for a real burden of diagnosis. It's psychological. It is economic. And there are some real morbidities with treatment, which I don't think I have to go through.

These are the issues that patients have to face. Is there an answer out there? Well, when you - when you look at the data, there is some important trials going on. There are two randomized clinical trials - the European study and PLCO. , and there are certainly a lot of numerous observational studies.

And many of these trials are conflicting. Patients can get one answer or another answer. And all the trials have design flaws. And clearly, none are going to inform the screening today in 2008. So what is the patient to do?

Well, as you saw from the slides that Dr. (Etzioni) so eloquently presented, we can give them some ideas of what would happen with and without screening. And I am not saying this is the be all and end all for a patient. It really does help a policy maker. But at least it gives the patient a little bit more information, and perhaps give some a bit more comfort either choosing to be screened or choosing not to be screened.

Another question, which the models from CISNET can really help us on is starting to identify which prostate cancers are clinically indolent. And for anyone who is in the clinical arena, active surveillance is a very reasonable treatment choice for some patients.

But the problem is, we don't know who they are. Clearly we know that some prostate cancers are indolent and are over diagnosed. And that is based on work that a number of the CISNET investigators have published.

But patients come in, and many of them know the old truism - more men die with prostate cancer than of prostate cancer. Certainly there are many doctors who say the same thing.

The problem is, as a clinician, and as a patient who is newly diagnosed. I can't tell you which patient is going to have been indolent cancer and which one is going to have an aggressive cancer. I have some hints, but in the end it is very

hard for me to conclusively tell a patient, I am pretty sure you are going to be okay. Or I am pretty sure you need treatment.

And it begs the question is there a way to identify tumors on a patient level that can inform decision making for the patient?

Now, there is some data out there - if you see this next slide. These are data from (Peter Albertson). He went back to Connecticut tumor (unintelligible) and looked at men treated with watchful waiting in the 1970's. And this is helpful to counsel patients. You can sort of stratify patients by their (Gleason) score, which is a pathological differentiation, their age at diagnosis. And based on that, you can sort of give them - give them an idea of what will happen if they choose to have no therapy. Vis-à-vis, will they die of their prostate cancer or not?

But the problem is that this doesn't take into all - account all of the variables. And it is dated information.

When you look at the existing data, (Peter)'s work and others - similar, all the existing data can account for tumor risk factors. But it is hard to account for host factors.

Age in an of itself is easy to account for. But not all 65 year old men are created equal. Some 65 year old man have co morbidities that makes them much more like a 75 or an 80 year old man and vice versa.

And finally, there are differences in race and other clinical factors, which I will call host factors, which the existing data can't account for.

But when you put all the data together into a model, this can allow us to combine these data sources and give us estimates that obviously inform policy making. But may also be useful to some degree for individual decision making, and may assist the patient and the provider at the bedside.

The $64,000 question in prostate cancer in my mind, even more so than who can go on active surveillance is which patients need aggressive intervention, and what outcomes can a patient expect?

And we sure have a lot of observational data to guide us here. And these studies compare numerous interventions, but the problem is when you look at these studies and you get under a hood as it were, you find the results are conflicting, and they are problematic. The studies often can't account for individual patient characteristics.

And that makes it tough for me as a clinician to go to the bedside and talk to a patient about counseling - for counseling. It is also frankly not always helpful to policy makers, because you cannot account for these individual patient characteristics.

I am going to show you two studies that short of back that point up. This is a study that was published two years ago by (Wong) and the senior author was (Katrina Armstrong) at Penn - that was in (unintelligible). They got a lot of play in the press and I had a lot of patients coming in. I am sure many of you are familiar with this study, using the (unintelligible) Medicare data showing that patients who have retreated with active therapy, whether it was radiation or surgery, did better in survival than patients treated with observation.

Well, this is fairly conclusive. And you see a survival difference within two to three years. But this study has a lot of problems. And there is issues with controlling for confounders.

(David Miller) and (Mark Littman) wrote a wonderful editorial to this study in (unintelligible). And in the end, you know, it is very hard for me to explain that to a patient, because there are so many other data issues, which the study doesn't account for.

One might say well, let's go to a randomized clinical trial. And we do have one randomized clinical trial that looks as surveillance versus surgery. This is of the Scandinavian study. I am sure many of you are familiar with this study.

And you can see that over many years, surgery does appear to have a survival advantage over watchful waiting. But it really takes about somewhere between 9 to 11 years for the curves to diverge - perhaps even later than that.

When this study was first published in 2001, I believe it was, there was no difference between the odds in overall survival. So again, we get into a problem here of yes, surgery is better for some patients - or I should say active therapy of any sort is better for some patients. But we don't know who those patients are. And clearly, some patients and don't need aggressive therapy.

And that is where the models can help us. And if the models combine the data from multiple sources - multiple randomized clinical trials. They can take into account different time periods. They can take into account for other additional factors.

And these may provide realistic estimates of expected outcomes with given treatments. And this is certainly helpful for policy makers. But I think it might also be useful for individual patient counseling.

I am not saying it is going to be conclusive and tell a patient you should do Treatment X or Treatment Y. But it is going to be a little more comprehensive information that will help guide the patient in the absence of the perfect study.

So to wrap up, I don't like there is any perfect answer to the clinical questions in prostate cancer. What I do know for a fact is that randomized clinical trials in this disease are very hard to do, and they often don't answer the question come completely.

And to this end, I think the models are very hopeful - not just for policy-making. But I think they inform decision making by providing additional information that can be useful to the individual patient, to the provider, but ultimately, as (Ruth) pointed out, to the policy makers.

And on that, I am going to wrap up, and I want to thank you so much for your attention.

James Hadley: Rocky?

Eric J. Feuer: Yes. Thank you so much.

Man: Back to James actually.

Eric J. Feuer: Oh, James, sorry about that.

James Hadley: Okay. We are now ready for questions. Operator?

Coordinator: Thank you. If you would like to ask a question, please press star then one on your touch-tone phone. Please record your name when prompted. If you need to withdraw your question, you can press star 2.

Once again, press star one to ask a question.

James Hadley: And we would like you to give your name and affiliation when you ask the question.

Man: And especially good questions relate to any questions that you might think of doing what the CISNET Group - prostate group, and you can ask about its applicability.

James Hadley: While we are waiting for a question, I want to remind you of the CISNET website. That's CISNET.cancer.gov. C-I-S-N-E-T.cancer.gov .

So I have a question. How accurately do the models really reflect the disease process? Models are often difficult to understand. And as a result, not easily trusted.

Eric J. Feuer: I know, (Ruth), do you want to try to answer that?

(Ruth Etzioni): Sure. So, it is a very good question. We - the first thing I want to say in response to that question is that the models are really a representation or an abstraction of the disease process.

We are not modeling the full biology of the disease. But we are modeling a representation of the disease at a level that will be useful to us in making the inferences that we need to make.

So for example, we are modeling PSA growth in the Fred Hutch model. And the disease progression, and this will - this is a level that we feel we need to model that in order to address the kinds of policy questions that I showed towards the end of my presentation.

Now, how accurately do we represent this level of abstraction of the disease process? There are several different levels of answer to that question.

First of all, since we are using maximum likelihood estimation, we can get estimates of our progression rates, and confidence intervals around those progression rates to get a sense of how variable our estimates are.

Ultimately, of course, the proof is in how well we represent the observed outcomes. We - I showed one slide that showed the calibration of the models to observe incidence.

And we do several levels of validation and calibration. And once we - and also by comparing results of the different models, we feel that we work together to reach a fairly accurate representation of the disease descriptions that we are describe - that we are using.

So in a way, you know, there are many different answers to the question. But I would say there is a formal statistical quantification of accuracy. And then there is a validation against the population, and a comparison between the modeling group that are all geared towards reaching a level of comfort with the reliability of the estimates.

And I think that is a really powerful aspect of CISNET is the working together of the groups. Not only do we - does that enable us to compare results, but it enables us to really improve our models and improve our modeling process so that we are really doing the best job that we possibly can with the admittedly imperfect data that we have.

Eric J. Feuer: Let me - I - This is Rocky Feuer. I could just add one thing to that.

And one thing we try to do is, when working together as a group, try to get as access to as many different data sources as we can.

And so perhaps, our data fits well to one data source, and then we try to fit it to another data source and maybe it doesn't fit as well. And then we try to understand what are the differences between the different data sources. Maybe a different health care setting. Maybe it is population data versus clinical data.

So by looking at more and more and more data sets, we sort of get a sense of how well we are fitting in different types - in different types of settings. And as one of the powers of having a group is that as we approach different groups for different data sources, they are more likely to open up and try to give the

data sources - at least in some limited way, to us so we can utilize them for modeling.

James Hadley: Did anybody else want to comment on that question? Thank you so much.

Again, if you have questions - we have a question. Questions. What is the question? Hello? Operator?

Coordinator: Yes, we do have a question from William Robinson of Black Men's Health Initiative. Your line is open, sir.

William Robinson: My question is regarding education. Has anyone thought about using this model as a means of tracking from education?

We educate black men. Lots of times in very rural areas in the southeast region of the country. And we are doing it through barber shop, churches and a bunch of other places.

And one of the things that has always troubled me is, because as I think David was talking about, we are not clear about how the efficacy of the screenings at this particular point.

And I am wondering, because we have this confusion, if that is actually contributing to black men having higher rates of prostate cancer? And I was wondering if the model would be applicable in a sense that we could put some kind of variable in regarding education and find out if they go to screening and later on follow up for treatment at how that might work, and what kind of data we would need to collect to facilitate something like that?

Eric J. Feuer: Dave, I don't know if you would be best to respond to that?

David Penson: Well, I think, you know, to date these models - I will do my best.

To date, these models have not been used in education programs for patients. But I do think that is one potential application as the models mature.

You know, previously, I think the models have focused primarily on the effective screening. And now we are moving further into the treatment area.

So I think it is - it is a really a ripe area for research. But more importantly for intervention. I think we could do a lot of good there.

And so - but to date, the answer to your question, as I understood it, was no we haven't used it yet in the educational setting - but I think it is a good application for it.

William Robinson: Okay.

(Ruth Etzioni): This is (Ruth). I would just add that the higher incidence in black men predates the PSA era. And the screening rates among black men - and especially among younger black men are similar and even greater than among white men.

So just (unintelligible) a point of information.

William Robinson: And that is what I want to impress. Because we have this confusion about when we should start screaming for black men. And begin to look at that and have some additional information that can inform the kind of decisions and the policy that is adopted for one when the - when black man should be initially screened.

(Ruth Etzioni): That is exactly the kind of policy that we would hope to evaluate - looking at different ages of starting screaming and different thresholds in this kind of work.

David Penson: Yeah, I would just echo - I was going to say what (Ruth) said. Yeah, this is probably the best forum to do - to observe - to examine questions related to race, because you are able to take so many different data resources that you are able to minimize in the selection bias.

I know that has been a focus of (Ruth)'s for some time. So I think that, you know, this is the perfect place to do what you suggested, Bill.

William Robinson: Thank you.

James Hadley: Okay. We have another question please.

Coordinator: And the next question comes from (Lisa Campbell) of East Carolina University.

(Lisa Campbell): Hi. I am a clinical psychologist and a health psychologist by training. And I design psychosocial interventions for men who have undergone treatment for prostate cancer to enhance adjustment.

And right now, my work has been focusing on men diagnosed with early stage of disease. Who have, you know, reasonable hope for, you know, a longer quality of life - a longer life and a higher quality of life.

My question is, to what extent has the models incorporated - enhances and sort of psychosocial treatment for prostate cancer and how that might impact the trajectory of recovery, surveillance behaviors, and other things that might actually impact survival?

Eric J. Feuer: (Unintelligible) go ahead, (Ruth).

(Ruth Etzioni): Well....

James Hadley: Yeah, (Ruth), you could talk about the potential. And then, David, maybe you want to comment.

(Ruth Etzioni): Well I - so the models at this point are only looking - have only looked at initial treatment decisions - essentially surgery radiation, radiation without (adjuvant) hormonal therapy. I am not sure if I am leaving any out.

So further interventions have not been evaluated. Now interventions can be added to the policy model. What one needs if one is going to add an intervention to the policy model is some kind of estimate of the impact of the intervention, say from a clinical study so that one is essentially has - is able to project results in the absence and in the presence of the intervention. And with a reliable estimate of benefit for impact.

And it could be impact only on the quality of life, if the model is projecting. At the moment, the models do not project quality of life. They project survival. But if the models are projecting quality of life and the impact is on, you know, if you have the impact on quality of life that could be added. Or if there is an impact on survival that could be impacted more readily.

But the potential is there, so long as the good estimate of impact our benefit, and also cost is available.

James Hadley: Dave, do you want to comment further?

David Penson: No, I don't have anything to add to that.

Eric J. Feuer: So these are the - this is Rocky Feuer again. These are the kind of enhancements that could be made to the existing - to the existing structure. And of course, it depends on the quality of data that is available.

(Lisa Campbell): Right. So the two studies I am conducting now are SEP interventions. One, I am looking at a group intervention. The other evaluating couples interventions. But we are not yet collecting economic impact data.

What would be ideal types of economic impact data to add to that treatment data?

(Ruth Etzioni): Well, I would say the cost of the intervention. And I am thinking that probably would be the one that is most critical.

If there is an impact, I - at the moment, in terms of incorporating economic outcomes, you know, we are looking mostly at cost induced by the intervention.

(Lisa Campbell): Right and primary (unintelligible).

(Ruth Etzioni): And treatment, and then any impact that might have impact on say, future treatment costs. So very direct costs of interventions.

(Lisa Campbell): Right.

(Ruth Etzioni): Those indirect costs, such as return to work, etc., you know, or productivity costs or gains or not at this point, you know, at least in the first level of planning for the expansion to economic outcomes.

(Lisa Campbell): Okay.

Eric J. Feuer: And I don't know if you are aware that, you know, the prostate cancer outcome studies (unintelligible) cost studies, which were done - which were sampled from the (unintelligible) database. Probably provides some baseline levels of quality of life, and morbidity, you know, morbidity from different interventions.

So sometimes it is nice to put interventions together with other studies that have been done. And we always - in the modeling always piece together various data sources.

(Lisa Campbell): Right. Well, Thank you.

James Hadley: Thank you. Another question? Operator?

Coordinator: Yes, the next question from (Wendy Fryer) -Holy Cross Hospital.

(Wendy Fryer): Good afternoon, everybody. And thank you for this very interesting webinar.

In terms of community outreach, is it possible to use these models as a decision model? Many times in the community, you know, where I asked about, you know, how the PSAs, you know, a lot of the points are brought up very nicely about, you know, the psychological concerns that this causes. And is there any significant change in survival?

And you know, there is sometimes costly and difficult to access. So is this something we can use to help people decide whether or not they should get a PSA?

Eric J. Feuer: Well, I will handle that one. Because I think ultimately the answer is yes. And, (Ruth), you can chime in. I don't think we're quite there yet. You know, we may be there for PSA screening to some degree.

I mean, you are - the models are able to feed in certain information for a particular patient and say, you know, given your age, potentially your comorbid status, and other issues, should you get a test? And if you were to get a test and you were diagnosed with cancer, how would that affect your outcome? Vis-à-vis, how much additional survival would you have or not?

But, you know, I think it is just a single piece of information to actually put together a decision analysis tree. You know, that - I don't know if we are there yet. And I have personally have had experience with that. I find that it is very difficult at the bedside to really - to explain the results to a patient and have them really absorb it. If for no other reason, if you go back to the decision analyses, it is all dependent on the decision that patients are coldly, logically and rational people.

And I don't mean that as a joke. But I mean that is actually one of the assumptions of utility theory. And patients who are considering screening and treatment decisions are not cold, rational, logical animals. They are - the decision is emotionally charged.

So I think you can give them some guidance. But I don't think that - (Ruth), you can agree or disagree. I don't know if these models are ready to be used as sort of a decision analysis tool per se. They may be useful for giving some useful information, but they are not going to spit out and say, if you choose to be screened, you are going to have an additional three years of survival, or three years quality adjusted life years.

(Ruth), would you agree or disagree with that?

(Ruth Etzioni): I think that a lot of the thoughts, have gone into these models and a lot of the work that has been done could be channeled towards that particular question, you know, to be screened or not to be screened. The majority of men have had a test. Or older men have had a test. And keep in mind in older men it is unusual. But (unintelligible) different older man who comes and says, should I have a test or not?

I do think that the kinds of - the kinds of components of an answer to that question overlap greatly with the components of we have already built for these models.

It is not exactly the question that we are thinking about, but I imagine that a lot of the work towards that questions we have already done. And ultimately, it would be an effort that could build on what we have built already.

(Wendy Fryer): Great.

Eric J. Feuer: Yeah, just let me just add - this is Rocky Feuer again, that the CISNET model, I think is both - everybody mentioned were primarily built for policy purposes and to understand population based trends.

But as you can see what - from (Ruth)'s, I think it was her final slide, we have been thinking about what it takes to bridge the gap between these models and decision support tools.

And I think, as (Ruth) said, we are part of the way there. And I think the CISNET group is starting to actively think about what is necessary to thoroughly go through that - to the thoroughly transform to that sort of thing.

So it is an area we are thinking about.

(Wendy Fryer): Great. Thank you.

James Hadley: Thank you. Does anybody else have anything else to add?

Coordinator: If you would like to respond, please press star 1.

James Hadley: While we're waiting, I will ask a question.

There is a lot of uncertainty inherent in the model development process. How do you deal with that?

(Ruth Etzioni): (Alex), (Eric), would either of you like to take that one? Or I am happy to as well.

(Alex Tsodikov): Yes, I think what you can say is that you are right. There is a lot of uncertainty in the modeling process. Still, I think, it is - the approach makes the best use of the information that is available in a sense.

(Ruth Etzioni): Right.

(Gerrit Draisma): I think there can be two directions there. So one direction is kind of building from the bottom up. So you are trying to use whatever information is available, and whatever data sources are available to get to population data.

So the other approach is more statistical. So you're going from the top and you are looking at the population data and are asking the questions, so what is the simplest model that you would be able to identify with these sources?

And I think the convergence of both trends is kind of one of the key benefits of CISNET.

(Ruth Etzioni): I would say there is a lot of levels of uncertainty. I think that multiple, that developing. One of the main sources of uncertainty is in the model that you build - the concept of natural history, and the decisions you make in the structure of the model.

And very often you only have one model. And, you know, maybe there is a sensitivity (unintelligible) some of the unknown inputs to look at some degree of uncertainty.

But it is very difficult to look at the uncertainty that comes from the way you develop your model. And CISNET allows you, by having the multiple modeling groups, allows you to get a sense of that uncertainty.

And that was very plain in Rocky's slide, where he showed the seven breast cancer models, which were really - every effort was made to make those models consistent, in terms of their caliber - the data to which they are were calibrated, the inputs, (unintelligible) patterns of the interventions.

And yet, there were still differences in the results. A lot of that, I think, comes from the uncertainty in the structural decisions made in the model development. But by having a multiple models, one can at least get a range of the uncertainty from those decisions, and I think that is very valuable.

James Hadley: Okay. Are there any other questions?

Coordinator: There are no other questions, sir.

James Hadley: Well, thank you so much.

Our want to thank each and every one of our participants today - especially those of you out there in the Web world who hung in there with us. We will have on that CISNET website, either this entire presentation or the slides and whatever. We will have to figure it out once we hear how this went off.

So again, I apologize for that. It was beyond our control. We really appreciate your participation.

We also want to thank those behind the scenes will have worked diligently to make this thing work. And the technical problems we have had today do not, in any way, reflect their work.

(Michelle Hathaway), who is the health communications intern in the Office of Advocacy Relations. Dr. Angela Mariotto, the mathematical statistician in the Statistical Research and Applications branch of the Division of Cancer Control and Population Sciences.

And also, Ms. Denise Buckley who is the writer and editor in the Division of Cancer Control and Population Sciences.

Ladies and gentlemen, we appreciate your indulgence and thank you so much. Good afternoon.

Woman: Okay. We are all disconnecting now.

Woman: Okay.

END