Stuart L. Silverman: My name is Stuart Silverman and on behalf of myself and our co-chair Bess Dawson-Hughes, I would like to welcome you to "Symposium E: Absolute Fracture Risk: An Update". Our goals this afternoon are as follows. We now have a diverse menu of effective osteoporosis therapies.

Our goal is to identify those patients most likely to benefit from these therapies, and as one of our speakers, Dr. Kanis has pointed out, we cannot afford to treat everyone. Let me spend a moment describing to you the current state of the art. You and I identified patients at risk of fracture based on bone density and risk factors.

Some of these risk factors are independent of BMD while others are not. These clinical risk factors increase relative risk differently. They differ in the ease in which we can measure or ascertain them. They differ in their response to therapeutic intervention.

We have not had a way to integrate these clinical risk factors in predicting risk in a given patient. As far as DXA or bone density is concerned access is limited globally. Approximately half of fractures happen in the community in individuals who may not have osteoporosis by Dexa using the 94 criteria.

What is our solution? The solution, which we'll discuss today, is to understand which risk factors predict fracture independent of bone density. We'll hear about a mega-analysis of multiple global cohorts to identify risk factors. We'll hear about ways to integrate these risk factors with or
without bone density to develop a model to predict absolute fracture risk. We’ll also hear that after the absolute fracture risk has been ascertained, intervention thresholds, either locally or regionally can be decided upon based on willingness to pay.

00:02:24
So our topics for discussion today are three speakers, led off by Dr. John Kanis who will talk with us about ‘Absolute Fracture Risk: The WHO Model and the European Perspective’, then Dr. Melton on ‘Concept of Fracture Risk and the US Perspective’ and finally Anna Tosteson, ‘Economic Considerations

00:02:49
and Absolute Fracture Risk.’ I’d like to tell you a little bit from a housekeeping viewpoint about our format today. Each of our speakers will have the opportunity of talking to you for 20 minutes followed by a five-minute question period and then at the end, Bess and I will be able to entertain questions for all speakers for 10-minute period.

00:03:12
I’d like to first of all introduce our first speaker, Dr. Kanis. John Kanis is at the Center for Metabolic Bone Disease, University of Sheffield in Sheffield. He is known to all of us as a leader in the bone field and I must point out, with sardonic wit, and global insight.

00:03:33
I have nothing but thank yous to John, it’s due to your leadership that we have the original WHO criteria, and now again under your leadership, working with all of us the new WHO absolute fracture risk model. John, we thank you.

00:03:59
John A. Kanis: Thank you Stuart for the introduction, which I must comment on and also I’m waiting for my slides to come up because I don’t know where they are, and thanks to the introduction.

00:04:19
I can’t wait to hear to what I am going to say. It’s also the role of the first speaker to test the AV system and there we are, great. Okay, what I am going to talk about is risk assessment and the background to that is, as Stuart outlined, the question is not how to treat patients because we have

00:04:48
a whole host of interventions that have been proven by double-blind placebo-controlled trials to effect significantly fracture risk. The question is, how do we target that? How do we identify an individual who would benefit from treatment, and conversely and as importantly, advise a patient that
their likelihood of fracture is low enough, so they shouldn’t consider a treatment at least in the immediate future? And the way that’s been done has been a little polarized between Europe and the United States. And in Europe, we depend on identifying clinical risk factors such as a prior fracture, such as family history of fracture.

On that basis, a bone mineral density is undertaken and if, depends from country to country, but if the T-score is less than -2.5, then that person is offered an intervention. If you think about that, that’s a very conservative scenario because somebody needs not only the risk factor but also

the...to qualify by the T-score and so it’s a conservative scenario, but it does identify very high-risk nations. In North America, the situation is slightly different. This is the algorithm for 65-year-old women and older. They do take account of clinical risk factors.

In the presence of clinical risk factors, a BMD is indicated, and where there is threshold, where the T-score is less than -1.5, treatment is recommended, so a big difference in the T-score threshold. In other words, more people would qualify, but at the same time have clinical risk factors.

On this other side of the coin, people without age 65 and over, without clinical risk factors are recommended to have a bone mineral density test and there the T-score is more stringent, a T-score of less than -2 would qualify for treatment. So, there are some fundamental differences in the conceptual thinking that in North America, for over 65-year-old women, it’s recommended that all women have a BMD test, whereas in Europe, this would be confined to those with clinical risk factors and the other difference is the way in which the clinical risk factors modulate the intervention.

But at the end of the day, these are all driven by decisions on bone mineral density. In other words, treatment is targeted ultimately on the basis of bone mineral density. Now bone mineral density is a usual test. It’s about as good as blood pressure to predict stroke.

It’s certainly better than hypercholesterolemia to predict myocardial infarction, but it is not perfect, and that’s shown in this slide here, which shows the...this is from Ethel Siris’ work. The number...the incidence of fractures and the number of fractures according to the T-score of peripheral bone mineral density.
What you can begin to see is that if you use a threshold, say of -2.5, then the risk of fracture is high. But relatively, a few members of the community fall into that category. So the vast majority of fractures will occur in those who you designate to be at low risk.

The same is true if you take a threshold of -2. The majority of fractures will occur in that segment of the community that you designate to have low risk. In other words, the detection rate of the test, or the sensitivity of the test is less than perfect for use in tackling the underlying problem of osteoporosis.

So the question that we have asked over the years is to say, can we optimize this sensitivity, can we improve sensitivity within either a screening or a case finding strategy? Can we franchise men as well as women, give men the vote? Can we rationalize that from a cost effective setting and can we do that with international rigor, if you like, that’s something that we can understand, how risk factor works in Japan as well as we can in North America. So the risk factors need to be validated in multiple populations. If they can’t, then this shouldn’t be used in an international setting.

We need to understand the dependence of the risk factor on age, on BMD; it’s dependent on other clinical risk factors. The factors need to be readily assessable by primary care physicians. There is no use doing a calcium intake, which you need a food frequency questionnaire that will last an hour, so you have to choose your risk factor.

It is to be intuitive rather than counterintuitive and a good example is dementia, which has a very high risk of fracture, but it’s not the first priority of a patient or a relative of a patient or a doctor to think about hip fracture in the context of somebody with dementia.

And finally, and as importantly, the risk factor needs to contribute to a risk that is amenable to a therapeutic intervention. How can we test that? Well, the best way to test that is to recruit patients on the basis of the risk factor. And we have many trials that have recruited them on the basis of low BMD, so that we know that patients selected by the risk factor of low BMD are responsive to a therapeutic intervention. But there are other scenarios within the context of primary trials, prior fractures, there have been trials where the patients are recruited on the basis of prior fracture.
or on the basis of the use of glucocorticoids and these outcomes have shown that patients selected on the basis of these risk factors respond effectively to an intervention. People haven’t recruited patients on the basis of smoking habits or markers of bone turnover, but what we have been able to do is to examine the Phase-III studies that are available and to see whether these risk factors adversely or beneficially influence the therapeutic efficacy of an intervention. And in this list here that I showed down here, these risk factors have been shown not to adversely nor beneficially affect therapeutic effectiveness.

So it’s second order or second level of evidence, and there are some risk factors that we are unsure of and an example would be risk factors for falling. Are we convinced today that treatment with antiresorptives in fallers is going to achieve a reduction in fracture frequency? The likelihood is yes, but the evidence really...base isn’t really there. So can we do better than the use of bone mineral density alone? And the answer is, yes we can, and we have known it for years, but we haven’t done anything about it. And this shows the relationship between fracture probability, hip fracture probability or the likelihood of hip fracture in a 10-year period, in women, according to the T-score, and the lower the T-score the higher the fracture probability, the well-established relationship between bone density and fracture probability.

But it is also evident that the significance of the T-score is quite different at different ages. For example, at a T-score of -2.5, the fracture probability is much lower at the age of 50 than it is at the age of 80. Indeed, the fracture probability is five times higher at the age of 80 than it is at the age of 50.

In other words, age is contributing to our understanding of what individual risk is over and above the information that is provided by bone mineral density. So we can improve the way in which we use bone mineral density by using this risk factor, namely age.

Now, over and above that, are there risk factors that we can add into these kind of algorithm? And the way in which we examined that was to look at population based cohorts from around the world, and these population based cohorts had bone mineral density measured, had some of the risk factors
assessed and then were let loose in the community and we were able to gather the primary information from these cohorts. So it's individual patient data from a large number of subjects from around the world. Constructing the models, this is about 60,000 men and women followed for about a quarter of a million patient years with about five and half thousand fractures in terms of the outcomes. So we...because this is an individual patient data, this has the strength of allowing us to interrogate the interaction of risk factors with each other, risk factors with age, risk factors according to sex.

Also, because these are primary observational studies, this eliminates really publication bias. Now, we can learn a lot about a single risk factor and this shows the relationship of BMD according to age. So, here is shown the gradient of risks, the increase in risk per standard deviation decrease in bone mineral density.

From the Marshall meta-analysis many years ago, we have in our head the increase of 2.6 fold in risk for each standard deviation decrease in femoral neck bone mineral density, and that's true in this analysis. But what's also true is that the gradient of risks, the predictive value of bone mineral density varies according to age.

So you have a higher gradient of risk at the age of 50, compared to the gradient of risk at the age of 85. So by having this kind of primary data, we can make better use of the tools of BMD than we could without that kind of information. Over and above that, there are a number of risk factors that turn out to have an independent contribution.

So here is shown the increase in risk with a prior fracture, family history, current smoking, corticosteroids, the use of alcohol, or rheumatoid arthritis, all showing a significant increase in risk and when you adjust for age and you adjust for bone mineral density, you can see that increase in risk persists.

So again, these are independent risk factors that can be used to improve the intelligence that you derive from bone mineral density and age alone, provided you understand the interrelationships between these risk factors. How does current smoking interact with the use of corticosteroids?

Again, you need the primary data to be able to do that. The other challenge is how do we integrate all this diverse information into a single measurement. Well, we could do that in terms of gradient of risk. We could do that in terms of relative risk, but nobody understands these terms.
We could do it in T-score equivalence, but the metric that is most useful I think to individuals is, what is the likelihood of fracture. And the likelihood of fracture depends not only on the hazard of fracture; it also depends on the death hazard. So the probability is a function both of the fracture incidence and mortality, and this is the reason why short-term probabilities and this shows 10-year probabilities increase in women in Scandinavia up to about the age of 80, then it begins to decrease. It’s not because the fracture incidence decreases in very elderly, it’s because the mortality risk outstrips the increase in fracture incidence. Men tend to live a few years less than women and so their fracture probability increases and then begins to dip at about the age of 80. So the use of probabilities allows us to integrate the information from all these diverse but relatively simple sources of information.

So, provided we understand the interrelationships of the risk factors, we can then formalize, if you like, the relationship between their age, relative risk and 10-year probability. And relative risk of one would describe the general community, let’s say, living by age, increasing up to about the age of 80 and then stabilizing at least in Sweden.

You can imagine that if you had a prior fracture you might have a twofold increase in risk and you’d follow this isopleth here. With a low bone mineral density, your risk might be increased twofold again. With a family history, it might be increased by 50% again.

And so you would follow this isopleth here. What you can begin to see is by improving the ability to identify high-risk patients with multiple risk factors, you can begin to select patients at truly high-risk where you couldn’t do that before and that’s something I will come back to.

Now, if we use the information then, and this shows the information of single clinical risk factors, then this is the probability, again in Sweden, of an individual, a female, Mrs. X, exactly at the age of 65. This would vary at the age of 66, or 70, or 80. The weight is this.

The BMI is exactly that. You can see that with no risk factors, the 10-year probability is about 2%. That’s lower than the average probability because on average, people have one or two risk factors, so it’s lower than average. And then with these individual risk factors such as smoking and
alcohol, there are moderate increases in probability, but with a prior fracture and the use of corticosteroids and a family history, these risks are relatively mild. So each of the risk factors has different weight and that weight...the interrelationships of those weights will of course differ by age, and in some instances by sex.

Notwithstanding, they are cumulative. So the more risk factors you have, the higher the probability. And this shows the relationship between body mass index and fracture probability in the absence of clinical risk factors, with the addition of a prior fracture, with the addition not only of prior fracture, but the additional use of glucocorticoids and the addition of a family history. And you can see that although the additions vary according to men and women and have somewhat different significance in men and women, they all have cumulative effects.

So they all add a little bit of extra information that’s provided by the clinical risk factors. That was shown in the absence of bone mineral density, but you can do the same thing even if you know or decide to measure bone mineral density. So again, we have decreasing bone mineral density, increasing the fracture probability and that in the presence of risk factors, a prior fracture, glucocorticoids and a family history, again you are getting increments in probability. In other words, you are adding independent information that allows you to characterize risk more accurately than you could in the absence of the use of those risk factors. Now, how does that translate and what’s the importance of that? And you can...one of the ways of looking at that is gradients of risk and this shows...it’s a hypothetical diagram, but it shows the Z-score, say a bone mineral density.

The lower the Z-score, the higher the risk of fracture and it shows two scenarios, one is the gradient of risk of 2.6. In other words, the risk of hip fracture increases 2.6 fold for each standard deviation decrease in bone mineral density. This is about the risk that we see for the prediction of hip fracture with femoral neck bone mineral density. The green shows the gradient of risk with a gradient of risk of 1.6. And 60% increase in risk for each standard deviation decrease in bone mineral density and this is about the performance characteristics of peripheral bone mineral density or DXA to predict any osteoporotic fracture.
Now let’s imagine that these two techniques you wanted to identify individuals with a relative risk of greater than three. That’s three-fold higher risk than the average risk in the population. Well, if you do that using a test with the gradient of risk of 1.6, the risk increases the Z-score, but it’s a small minority of the population about 0.2% that you would identify to have a risk above that risk threshold of a relative risk of three. With modest improvements in gradient of risk in this example, 1.6 to 2.6 you can see the risk increases with decreasing Z-score and we can under this scenario, identify about 16% of the population above a relative risk of three. So it shows that relatively small changes in the gradient of risk have a marked impact on sensitivity, the ability to detect those individuals who will genuinely fracture within a given timeframe.

If we look at the performance characteristics, say a bone mineral density alone, as I showed you earlier, the performance characteristics are quite higher at younger ages than at older ages. But if you use clinical risk factors in conjunction with bone mineral density, you can see there is a significant increment in risk irrespective of age.

Its not large, its not doubling the gradient of risk, but the small increments that it is producing is having a very significant impact on sensitivity. And the same is true not only of hip fracture, but also of other osteoporotic fractures and the addition of the clinical risk factors enhances our ability to detect high-risk patients.

So how can we translate this into a case finding strategy? Well, we take account of the clinical risk factors. These cost almost nothing to attain and we can assign a fracture probability. There will be some members of the community where the fracture probability is so high that you are going to treat them irrespective of any knowledge of BMD.

If somebody has had two or three fragility fractures, you are going to treat them. They have osteoporosis; they are going to respond to intervention. Conversely, there will be some individuals where the probability is so low that you might not consider to do a BMD.

And an example might be a 50-year-old woman, normal menopause, no risk factors, who comes by hazard to the surgery and says, "I am concerned about osteoporosis." And then an intermediate group, where you might say, well my intelligence or ability to stratify risk is going to be enhanced by knowledge of BMD.
So you measure a BMD test, you reassess the probability in the light not only of BMD, but also the clinical risk factors and to assign people into high and low priority groups. How big is that intermediate group? Well that depends from country to country.

In the United States, it’s recommended that all women over the age of 65 get a bone mineral density. So the intermediate group is going to be rather small. In the UK or in other developing countries, bone mineral density is rationed. And people will begin to have to device algorithms to say how are we going to ration that that we can get the biggest bang for our buck out of bone mineral density. So when I talk about the European or US or global perspective, we are talking about the same thing. We are talking about the use of clinical risk factors, assessment of probability, where you can afford it with the use of BMD and when you can’t in the absence of BMD. Ultimately, you are going to have to decide who is at high risk and who is at low risk and who you are going to treat, and who you are not going to treat. And that’s something that comes from local priorities from the wealth of the country, the GDP of the country, the percent of the GDP that’s spent on healthcare, the problem that osteoporosis has in the community, is it a big problem, is it a small problem, these are local issues and the idea here is to provide a reference or platform technology on which those basis, those local decisions can be made more rationally.

And let me just finish by giving you one example of a woman and this based on the health economics of the UK. A woman aged 65 with exactly a BMI of 24, if you consider rheumatoid arthritis, the use of glucocorticoids and a prior fracture, you can assess probabilities in this case in the absence of BMD and there are (inaudible) scenarios show where, with the UK health economics it would be cost effective to treat and the black scenarios, where it would be less or not cost effective to intervene. That’s not something that is necessarily translatable to any other country or indeed any other age, but it shows that we have the ability to use this reference technology to turn the technology into something of practical use. So I will leave you with the thought that case finding or screening today with the use of bone mineral density is sub optimal.
It’s directed by BMD, but we have with relatively simple tools, the ability to add in value, the value of BMD or the value of BMI, by the use of very simple clinical risk factors, because we are now in a position to understand the interdependence of all these clinical risk factors.

By so doing, we can improve the sensitivity of the technique. We can improve the detection rate of high risk patients and therefore, we can direct our interventions more optimally and use our money more wisely to target interventions at those who can identify to be at high risk that was hitherto impossible and as importantly to exclude interventions to those at low risk. And the European perspective, to me, is exactly the same as the US perspective, save for the question of rationing. Thank you.

Stuart L. Silverman: Thank you John. We have a few moments for questions. Are there questions from the audience? Microphone 1.

Male Speaker 1: I’m (inaudible) Abrahams in Copenhagen. Surely, this is really important, there is one thing I can’t follow and that’s the independence of risk factors, because surely we know that patients who are treated with glucocorticoids are more likely to sustain fractures. So how can we build into the model that glucocorticoid treatment and prior fracture are independent in prediction of fracture, because surely you are more likely to have had a prior fracture if you have been on glucocorticoids?

John A. Kanis: Yes, I mean, you are quite right. What you need to do is to be able to look at the risk of glucocorticoid treatment independent of the prior fracture, and of course that’s the kind of information we were able to extract, so we can use those as independent risk indicators.

Male Speaker 1: So, just to clarify, so you had actually shown with the data that you have that you can use a model that assumes these things to work independently.

John A. Kanis: Sure.
Male Speaker 1: Thank you.

Stuart L. Silverman: Microphone 3.

Male Speaker 2: Thank you for an excellent talk. The WHO model appears to be a good tool to predict who will fracture.

However, as you mentioned in your talk, many of the clinical trials did not select patients based on some of the risk factors in the WHO model. Given that many future decisions at least suggested that should be based on cost effectiveness analysis, what kind of assumptions are you...will cost effectiveness models make for subgroups for which there is no data on clinical efficacy?

John A. Kanis: Yeah, I wouldn’t say there is no data. What I am saying is that...

Male Speaker 2: Limited data.

John A. Kanis: Well, it’s limited, but it’s quite reasonable. I mean, if you can demonstrate, for example, the therapeutic responsivity to agent X is the same in a smoker than in a nonsmoker, this is reasonable presumptive evidence. It is not the highest level of evidence, but it’s reasonable presumptive evidence that we can utilize that risk factor. So, all the risk factors that we have utilized have either gone through the grade of the highest level of evidence or the second level of evidence. And we haven’t used any risk factors where we don’t have any evidence.

So I accept the criticism, but that’s...the caveat is that there is some evidence, it might not be the highest level of evidence.

Male Speaker 2: Thank you.

Stuart L. Silverman: Thank you.
Bess Dawson-Hughes: Good afternoon, I'm Bess Dawson-Hughes and I would like to introduce our next speaker, Dr. Joseph Melton who is well known to most of you. He is the Eisenberg Professor of Medicine and a senior consultant in epidemiology at the Mayo Clinic in Rochester, Minnesota.

He is the author of over 450 peer-reviewed articles and over 1100 total publications. He will address the topic of instituting the absolute fracture risk algorithm in the United States. Joe?

Joseph Melton: Thank you Bess for that. I think what those numbers tell you is there is not much else to do in Rochester.

And what John just explained to you provides us with an opportunity to resolve some practical problems in osteoporosis management and maybe rationalize our therapeutic strategies even further. So let’s go back to what the problem is here. As you all know, the elderly population in this country and around the world is increasing rapidly and as a consequence, it’s predicted that there is going to be an enormous increase in osteoporotic fractures that occur each year that burden the patients obviously and represent a societal burden in treating those fractures and caring for their complications.

If you want to have any big impact on reducing those future fracture numbers, we have to treat broadly in the population, because almost everyone in the population is at risk of osteoporosis at least to some degree, and that includes men and nonwhite populations.

But as you have already heard represented, we can’t afford to treat everyone and that’s illustrated in this analysis that John Kanis did, where if you assume a cost effectiveness threshold of $30,000 for quality adjusted life year saved, and you are looking at an intervention that reduced risk by about a third, if you had a treatment that cost $625 a year maybe something like a bisphosphonate, its not cost effective to treat average risk women in the population until they are 80 years old. Now, Anna is going to talk a little bit more about this later, but I want to make this point, why is that?

Well, if we are looking at the 10-year probability of any fracture in women in different ages...here is this average risk 80-year-old woman and her risk of an osteoporotic fracture in the next 10 years is about 21%. It’s not cost effective to treat these average risk 50-year-old women, because their
risk is only 6%, so there are less fractures to avert and less savings to be had. But look over here, if you could find that subset of 50-year-old women whose risk of fracture was fourfold greater than that of their peers, their risk over the next 10-year is 21%, the same as those 80-year-old women.

And the same thing for the 60-year-old women who are threefold greater risk than their peers or the 70-year-old women who are twofold greater risk than their peers, and also for high-risk groups of men. If treating these women is cost effective, treating these high-risk groups is probably cost effective as well.

So, how do we identify those high-risk groups? I borrowed this slide from Mike Lewiecki, who reviewed different practice guidelines and found that basically all of them thought that it was sensible to treat patient who presented with the fracture. All of them also thought it made sense to treat patients who present with osteoporosis by WHO criteria, BMD less than...T-score less than - 2.5 and they all agreed that it probably wasn’t reasonable to treat low risk women on the basis of their BMD score and low risk factors. In between here, people are using BMD scores and risk factors and this seems somewhat coherent until you realize that nobody agrees on what risk factors to use and this is not operationalized. Where is the clinical tool that makes it easy for the clinician to integrate the risk factor data with the BMD data? Okay, and John showed you this slide just a moment ago, although I want to make some different points about it. These are data from the NORA study, enormous office based position. A set of women, where their BMD was mainly measured with peripheral devices, showing that the risk of fractures goes up as the BMD values go down and John pointed out that when you actually look at the number of fractures coming out of these different BMD groups, it was actually greater here in the osteopenic group than it was in the osteoporotic group, because so many more women were in these other groups. So for example, only 6 % of this population was osteoporotic, 39% had osteopenia.

So the issue right now then is, what do we do about this? Okay, so here is our osteoporosis definition. We identified an intermediate risk group, the people with low bone density or osteopenia, and we were roundly criticized for this. But osteoporosis is not unique among other diseases.
So for example, you have got exactly the same problem when you are defining hypertension and thinking about the risk of stroke. You have exactly the same problem when you are defining diabetes on the basis of blood sugar measurements to try to think about preventing complications of diabetes and what did those diseases do?

It’s the exact same thing. They invented an intermediate risk group called, what? Pre-hypertension, pre-diabetes, exactly the same as osteopenia. Okay, what those groups also did, because they recognized that the sensitivity wasn’t very great, they changed their diagnosis threshold and so it was

many years ago, the American Diabetes Association changed the blood sugar level that defines diabetes. And if you are old as I am, you know that they have changed the definition of hypertension four or five times since 1950. Okay, that solves the problem in part, of increasing the sensitivity of the test, but it comes at the specificity.

And so you end up managing, treating more women, but who are at lower risk and less able to benefit from that therapy and so as John pointed out, what you really need here is a better test. This is a complex slide, but I think it helps think about how the better test works and John showed you another representation of these same kind of data.

So let’s say you are trying to identify that subset of the population, let’s say these 50-year-old women who are at threefold greater risk of fracture than their peers. And you have a test with a gradient of risk per standard deviation change of two, but that’s something like peripheral BMD all by itself.

And if you apply that test to your population in this particular data set, you would have identified about 3% of that population to be at high risk and the average relative risk within that group would have been four, but let’s say you wanted to improve the sensitivity or you could lower the threshold that you are looking for and if you did that, you would increase the proportion of people who we said to have a positive test and at high risk, but you are reducing the specificity, and you can see that, because the average risk within that population is going down.

But if you had a way better test, one with a gradient of risk per standard deviation change was not two but five, and John just showed you that the gradient of risk per standard deviation change of the WHO algorithm in 50-year-old women predicting hip fracture is five not two, then what do you do?
Now, you are still trying to identify that same high-risk group, but now you identify 7% of the population to be at the target population and you cannot reduce the specificity. You have increased it because average risk within that population is not four but now eight.

And we have known for decades that the way to improve the gradient of risk with the test is to add the clinical risk factors to the BMD. These are data from the study of osteoporotic fractures from 1995. That’s what, 11 years ago from Steve Cummings showing prospectively in elderly white women that

the risk of hip fractures per 1000 person years goes up as BMD, in this instance measured in the heel, goes down or as the number of clinical risk factors goes up. But you can see that the best gradient of risk combines both things and so the gradient of risk with clinical risk factors added to BMD is 10 fold better in this particular instance.

So what’s the problem? We have never been able to agree on a set of risk factors. And here is just one review pointing out that there are dozens, and dozens, and dozens of risk factors have been identified and new ones are being identified everyday, especially when we are looking at genomics and proteomics.

So how could the WHO fracture risk prediction algorithm help with this problem? As John pointed out, they got individual level data for most of the big epidemiology studies in the world at the time this was done and of course those individual level data were anonymized, but this is not just a meta-analysis of average results from studies.

This was the whole pile of individual subjects, enormous numbers of them with huge numbers of fractures seen and so they could identify a robust set of predictors that seemed to work around the world for men as well as women and for people of other races besides white, although there weren’t so many data about that.

There are some subtleties here too. He got a WHO working group convened to do this work, but he got the NOF and the IOF to agree on the strategy and this set of risk factors, which I assure you is no mean accomplishment and so buried underneath a set of risk factors is the notion of global

consensus moving forward, which will help all of us when we interact with the payors (ph). But this was not the first absolute fracture risk algorithm. The NOF developed one in 1998 that provided the basis for the current osteoporosis practice guidelines and it had these risk factors in it compared to the WHO.
The WHO dataset was so much larger that they were able to identify some additional independent risk factors to put in the model. And that was actually really important because the ones they identified with corticosteroid use in secondary osteoporosis, which I submit are the kind of patients you might most want to treat.

But for the average person in the population, for the average patient, once you have all of these risk factors in the model, additional risk factors don’t contribute too much. And so it is my personal hope that by implementing the WHO fracture prediction algorithm, we will not have a disruptive effect on the practice guidelines that we currently have in place. So what are the practice implications? From this algorithm, you will get, although it’s not totally clear at the moment how you will get this, that’s being negotiated, something like this.

Based on this particular patient’s BMD and that person’s personal set of risk factors, what is the probability of an osteoporotic fracture over the next 10 years and how could you use that? What does it mean when you tell a patient I have a treatment that can reduce your risk of fractures by a third?

What does that mean? Well, if you are talking about that average risk 50-year-old woman, it means that that treatment might reduce her risk of an osteoporotic fracture over the next 10 years from 6% to 4%. I think patients can sense this that the risk isn’t very great.

The benefit is not very great and I think that’s why compliance to the prescription and adherence to therapy long term is problematic in this group. What about that 60-year-old woman at three-fold risk? Well, now her risk might be reduced from 26% to 17%.

Maybe that’s a motivation for this person to adhere to therapy. Now, there are three implications of this. The first is that this approach might end up putting the right people on therapy or at least the women more likely to benefit i.e., these people and not those people.

And certainly absolute fracture risk, is I think, an easier way to communicate this information to the patient and trying to explain the T-score because I don’t think any patient and hardly any physicians understand the fracture risk implications of the T-score.

The second implication is that when you tell the person you are going to reduce their fracture risk by a third and show them this information then it becomes clear that their fracture risk is not going to zero. It’s just being reduced by a third and I know that my clinical colleagues are plagued
with patients on potent therapy who have a fracture and come in under panic because they need another drug added to the regimen because the first one failed. We don’t have any treatments that reduce the risk of fracture to zero. So I think this will help at that problem.

But this is not just a communication issue, going from T-scores to absolute fracture risk. It’s actually a sea change when you go from communicating risk and benefits in relative terms, I can reduce your risk of fracture by a third to absolute terms.

And this problem is being encountered in other diseases and I give you here, an example from the cholesterol world developed by some of my colleagues at Mayo, Victor Montori and his group. They have created a model just like the one we were talking about that predicts this person’s absolute risk of fracture and gives them a personalized score sheet that looks like this and so this particular one is for a woman who has a 15-30% risk of having a heart attack in the next 10 years, very analogous to that 60-year-old woman we were just talking about a while ago.

And they show the effect in absolute terms of taking a statin or not taking a statin on this heart attack risk. And down here, you can see these orange ones here are the heart attacks and over here, the heart attacks with the yellow one showing the heart attacks that were prevented by therapy.

And this drug then prevented their heart attacks by about 25%, again analogous to what we just talked about. But the patient sees this picture and they can see that 80% of the time, nothing is going to happen whether I take this drug or not. And so, the challenge we will have is patients being empowered on the basis of absolute fracture risk to understand the implications of therapy in a very real way and many of those patients will look at data like this and decide to forgo therapy and that decision may not be rational. And so this is a big patient education motivation problem that we are going to have to deal with those few.

So why is any of this important to finish? That’s because there is enormous increase out in the community in diagnosing and managing osteoporosis and these data are from a large representative sample of office-based physicians in the United States showing what happened from 1994 when the first
An operational definition of osteoporosis was created by the WHO to now these people reported a 10-fold increase in the number of osteoporotic patients that they recognize. They said, ‘Well jeez! All along we treated everybody.’ This is self-report remember. I don’t actually believe this.

The treatment here accounts calcium and vitamin D so maybe, but you can see that there is enormous increase in the use of potent therapies bisphosphonates and SERMS especially, and there is the hope then that the WHO fracture prediction algorithm will help assure that it is the right patients being put on these treatments.

So because of the aging population, number of fractures that we experience will increase unless we do something better about intervening. We have two things to do about that. One of which we haven’t talked about there and that is public health measures, which are applied to the entire population without respect to the patient’s risk like vitamin D on the milk and calcium in dietary products where you don’t need to evaluate the individual. Public health measures got a boost in the recent Surgeon General’s report on bone health and osteoporosis and we should all as physicians endorse public health measures.

Because no matter what public health measures are in place and they are not actually many, there will always be patients who fail those public health measures and so there will always be a need for what we do, which is the clinical approach to case-finding, identifying, and treating high-risk individuals.

In that respect, the current intervention thresholds T-scores are sub-optimal because there are confusing to patients and physicians. And they miss a substantial number as you’ve just seen of high-risk patients, who actually experience fractures. The WHO approach estimates absolute 10-year fracture risk and this should help with that decision-making, and efforts are underway around the world then to adapt current national guidelines to take advantage of this new tool. Thank you very much.

Stuart L. Silverman: Thank you Joe. We are open for questions...we have a few moments for questions.
Joseph Melton: As though...anybody goes to the podium, to the microphone side, actually I'll discourage it, but you need to speak up and speak clearly because my hearing is really bad and getting worse.

So you may have to help...have to help.

Seth Rosenberg: My name is Seth Rosenberg from Brussels. Hi. Just a comment and you are right to say that absolute risks are quite important, but there is also another dimension, which is the time that you use for this absolute risk. If you want to motivate your patients to take a medication, you will rather use a 10-year risk fracture. If you want to speak about a side effect and you want to, you are afraid that they will not take the medication; you will rather use a five-year period of time because absolute number would be much lower. And this is, I think there is a dimension of the amount, the absolute amount, that is very subjective and the patient probably would be very focused on that number and will lose the aspect of the time spent on that. I don't know if I am that quite clear about that.

Joseph Melton: Okay, I missed most of that, but that is about patient values.

Seth Rosenberg: I gave the example with hormonal replacement therapy and breast cancer...

Joseph Melton: Ah...yes.

Seth Rosenberg: ...for instance.

Joseph Melton: That's an issue we might discuss later. We had this debate for a long time. Clinicians would prefer to know the fracture risk right now thinking that, that motivates the patients the most, but if you say what is the cost-effectiveness over one year, no treatment under any circumstance is as cost-effective.
And so, the problem then is you have the physicians on one side wanting to know the immediate risk and the payors on the other side wanting to know the real benefit they are likely to get from this expenditure. So this is a compromise, but the minute you go to shorter durations, the payors will turn on you and say that we cannot justify the use of any therapy. So, it’s a political compromise.

Stuart L. Silverman: You go...microphone 1.

Male Speaker 3: I am surprised that you concentrated so much on the treatment approach when we have compliance with therapy that lasts approximately 3 to 12 months, where after which 50 % of patients are no longer taking medication. Therefore, what is the point of calculating a 10-year risk? Do you think that we should be trying to move whole populations without drug therapy and this ultimately, if successful, might be better?

Joseph Melton: Okay, as best I get that through your thick accent there.

Male Speaker 3: Well, I spoke slowly for you.

Joseph Melton: Okay. You hardly have to have any accent to befuddle me. Okay, we have two different things going on here.

The public health perspective is you can’t justify any of this treatment with these expensive drugs because the only way to impact on a problem like this that will fix the whole population is public health measures. The problem is that public health measures aren’t in place.

Okay, so we do need to work on the public health measures. How many people in Philadelphia are vitamin D deficient right this minute and what does anybody in Philadelphia doing about it? Okay, the other issue though is we do have to work on making our treatments better.
And so, when you talk to policy makers, who are smart people even though they don’t always agree with us, they look at those adherence rates and they say that this isn’t going to pay off. I am not going to get any benefit from paying money to work these patients up and putting them on these drugs if they don’t stay on it.

Part of the problem, I think is we didn’t put the right people on it, but we do have to work on the adherence. So, that is the ‘Achilles heel’ of our field and is worthy of serious attention from all of us.

Stuart L. Silverman: Microphone 3.

Female Speaker 1: This absolute risk assessment to identify people who are really needy of treatment does not, I feel, address the woman who is losing bone rapidly in the fifth decade. And to apply this risk and saying that their risk of fracture in that decade is very low, but that’s the person who is losing bone rapidly and it’s in a very preventable mode of thinking. I do not understand how we can apply this to that population?

Joseph Melton: You understand that correctly the...

Female Speaker 1: Like in that decade, we should be...

Joseph Melton: No, I understand...

Female Speaker 1: ...addressing bone loss, not necessarily fracture risk.

Joseph Melton: These...the people who are at high risk of fracture could be the people losing bone, but you know, we have problems representing that rate of loss. What John didn’t tell you is that this is a living creature here and efforts are being made to incorporate other things, for example biochemical markers of bone turnover, which would help you evaluate the rate of loss issue. We are still dealing with the policy makers in terms of how precise serial BMD measurements are in terms of predicting the rate of loss and that’s not trivial either.
So I would say that if we had a way to identify people who seem to be losing bone rapidly, even if it was separate from these risk factors, we would want to integrate that, but remember, this whole exercise is driven by the World Health Organization. This has to work in the entire world, not just United States, and it has to work in places where there is not a lot of technological backup. And so, I think in answer to your question, this is the first approximation and I think all the clinicians here appreciate this problem, but we don’t have an easy way to incorporate that into a risk assessment at the moment.

Female Speaker 1: Because such an algorithm may persuade people who are payors. We don’t even address doing bone densities in that age group between 50 and 65.

So that might take us away from that if we put a lot of thought into this.

Joseph Melton: If you want to talk more...come up and I can understand.

Stuart L. Silverman: I am sorry. We can’t take further questions, but we have about 10 minutes at the end.

Joseph Melton: Thank you.

Bess Dawson-Hughes: Thank you very much. And our last speaker is Dr. Anna Tosteson. She has medical degree and a Ph.D.

in Statistics from Harvard University and much experience in economic modeling. It’s a great pleasure to have her, to hear her perspective on the issue. How we apply economic reality in the United States to absolute fracture risk. Anna?

Anna Tosteson: Thank you very much Bess. The usual disclosures out of the way first. The question that I am going to first begin by addressing is why are the economics of osteoporosis intervention important?
And it turns out to be fairly simple to answer this in that certainly osteoporosis treatment is of healing. Fractures are very costly in both human and economic terms. There is certainly no controversy about that. We know we have effective treatments to reduce fracture risk.

We have effective tools for assessing risk, but unfortunately, some of the interventions for osteoporosis are relatively costly. And in this era of constrained budgets, this motivates interest in identifying economically viable interventions; interventions that provide good value for the resources invested, ones that are cost-effective.

Now I think I would like to elaborate on this a little bit in the US context by looking at Health Care spending in the US. Last year, the US Gross Domestic Product or GDP was 41,000 per capita. Health Care spending at nearly 7,000 per capita accounted for 16% of per capita GDP, which is quite a substantial proportion of spending, and this is projected to double in the next decade. So, from the perspective, the US Government payer perspective Medicare, the Medicare program finances much of the elder health care in the US. This is a tremendous problem.

And as this figure shows, we have here, percent of GDP over time, in this graph from the Congressional Budget Office, we see that is spending on health grows at a rate faster than the GDP. We see this enormous growth in spending and there is a real reality to the situation in that we can’t afford to spend money on everything, and we have to spend our money wisely so there is great interest in economic value. Well, where does the rise in real US per capita Medicare spending come from? We have one study or a series of studies that looked at this over the period of 1987-2002 and really came down in defining two broad areas where we could attribute this rise to. One was an increase and the cause for treated case, over here about 27% of the increase in cost over that period, but the large share of the increase, nearly 63%, had to do with an increase in treated disease prevalence.

Well, what factors have to do with that? Certainly, population factors could lead to increases in treated disease prevalence. For example, the aging of the Baby Boomer Population in the US. Certainly, health care innovations, new technologies, new treatments can contribute to the growth of cost in both areas.
Of interest, particularly for today though is this notion that treatment thresholds could be contributing to the rise and treated disease prevalence is something that we have to think carefully about and certainly pay attention to as we think about changing where establish thresholds may be,

although I think many of us in this room would agree that certainly, there are populations where we have under treatment right now in osteoporosis, and I think these data show that a little bit. This study looked at age-adjusted treated disease prevalence in Medicare beneficiaries over the same time period, and we show here this is osteoporosis starting around 2% in ‘87 going to about 10% in 2002, and compared to hyperlipidemia, shown in red here, had a much faster rate of growth in treated disease prevalence for high cholesterol, and hypertension had a rise...a slope similar to the rise for osteoporosis, but treatment at much higher levels. One thing that happened over this period for hyperlipidemia, in addition to there being new advances in pharmacologic agents being available was a big effort by NHLBI to promote cholesterol guidelines through the National Cholesterol Education project.

So, without this background, I am going to turn to the question - what form of economic evaluation is helpful here and for that, we are going to turn to cost-effectiveness analysis, and the objective of this kind of analysis, this quantitative framework is to assess the relative value of health care interventions, and the rationale is that with limited resources, each intervention should provide a benefit worth its additional cost. So, in this form of analysis, we look at measuring the cost per unit of health gained and we focus on something we call the incremental cost-effectiveness ratio or ICER, we measure the net cost of an increase relative to net effectiveness, and the effectiveness measure we focus on typically, I mean, interventions especially, in health medicine in the US and actually, internationally now involves QALY’s or quality adjusted life years.

We account for both length and quality of life. The kinds of cost that go into these analyses include the cost of treatments as well as those of fractures. So, what is cost-effective on this ICER or cost per quality scale and this figure shows that a spectrum ranging from very favorable ratios
down here at the bottom less than 25,000 per quality gained to pretty unfavorable ratios up here over 125,000 per quality gained. There is a great deal of debate about where we really should be drawing the line and where people do draw the line, but quite a bit of what’s done in the US Health Care system falls kind of in this yellow, in this zone, right in here. Interestingly wow! That was interesting. I don't know what just happened to the PowerPoint presentation, but...there, you have to be careful where you click. A couple of weeks ago, some of you may have heard about this piece by David Cutler that appeared in the New England Journal of Medicine. The sound bite from this article was that we are getting good value for money for resources invested for spending on health care in the US, but if you look at this a little more carefully and look at the longitudinal trends in terms of cost per year of life saved or per year of life gained, by age range, we see that we have, in the older population here, 65 years and older, these...the spending is going up and the value is not exactly very good. We have ratios of 150,000 per year of life saved. This is per year of life saved rather than per quality-adjusted year of life saved, but nonetheless, it’s a reason for little bit of concern. So what role have such analyses have in osteoporosis guideline development? Well, they have had a role, you heard about the previous NOF guidelines were supported by an extensive review of evidence on prevention, diagnosis, and treatment and an economic evaluation on that, David Eddy conducted at that time. And, you might be asking about now, should economic considerations affect whether you would actually treat a postmenopausal 55-year-old woman who has had a prior fracture or a 65-year-old woman with a T-score of -2.9 or how about a man who has had a prior vertebral fracture and I am going to ask that you indulge me for a minute and certainly, the notion that risks drives appropriate clinical action is one that I think many people in this room are comfortable with. You may not be used to looking at on an expected value scale where I am going to show you a graph that any of you who’ve studied decisional analysis will feel familiar with, where we see expected value in terms of health or quality adjusted life expectancy ranging from poor to excellent, the
probability of a target disease, ranging from 0 to 1 and we can see that if we intervene in a population, the benefit we get from treating if the disease is bad, increases as the probability of the target disease increases. Likewise, if we choose to follow someone and the chance that they have the disease of interest increases, their health or general outcome might deteriorate and typically, in between, we might need to do a test to decide whether we should just follow someone for a while or intervene. Now, these relate to some important thresholds, a No Test-Treat Threshold and a Test-Treat Threshold.

And these are...this whole model and way of thinking about things, I think was written about by Jerry Kassirer and Stephen Pauker in the New England Journal of Medicines several decades ago, but the idea here is that economic considerations should drive where these thresholds are drawn or in an era, where we have constrained health care resources, we need to bring economics into the picture to help us decide where to draw the line. So, the 1998 NOF US Analysis did do this and they did this by taking the probability of various fractures, given age, BMD, and other risk factors along with the fracture consequences, the costs, and outcomes, and looked at the effectiveness of the treatments for preventing fractures, integrated the cost of treatment and used a cost-effectiveness threshold of $30,000 per quality adjusted life years saved. And that analysis was done in 1992 dollars, if you were to inflate it to present date dollars, that threshold would be about 50,000 per QALY. Subsequent to that, Dr. Kanis really formalized this approach and wrote about the idea that we should base osteoporosis intervention thresholds on this form of analysis, perhaps not looking at each specific agent, but looking more broadly at the general notion of should we intervene or not and how does the risk, what does risk have to do with it? In this slide, Dr. Melton showed before that we had the $30,000 per QALY threshold, and the point here is that in this paper by Dr. Kanis, you could see that the intervention threshold would vary quite a bit. The age at which you would intervene on average risk people intervene...vary quite a bit on the basis of how much the actual drug cost. Subsequently, Dr. Kanis' published Intervention Thresholds For Osteoporosis in the UK,
there have been an analysis reported as well for Sweden, but what we see here is that these 10-year risks are estimated for each age and they are linked with an economic analysis suggesting that intervention in that group provides good value for the resources invested.

So, how does comparison of the recommendations across the different analyses that have been done today go? Well, I think it’s somewhat reassuring to see that there is a fair degree of comparability, really quite a bit of comparability. Should you treat postmenopausal women with an osteoporotic fracture?

Yes, across the board. What about women with osteoporosis by measuring their T-score? Yes, across the board. Also, women over 65, who are roughly at average risk? Yes, in the current US and the new Swedish analysis. If you are about 80 in the UK. What about people who are postmenopausal?

It goes on from there, but there is a fair bit of agreement across the groups who have looked at this. So, how will an updated US case differ from earlier analyses? Well, first we are going to use, we would use the best available US data, best available evidence to look at the probability of fracture given age, BMD, and risk factors.

The fracture outcomes, both cost and QALYs, can be updated with more recent evidence. The treatment effectiveness could be updated and we might consider a slightly higher cost-effectiveness intervention threshold of 60,000 per QALY gained. So, how is absolute risk used in this endeavor?

Well, first the cost-effective intervention thresholds for specific subgroups of interest on the basis of age, sex, and race or other risk factors are defined on the basis of absolute risk, and then, we use specific risk profiles that...we examine specific risk profiles, hopefully, ultimately using the tool that Dr.

Kanis described earlier on, so we can find who, it would be cost-effective to intervene on. So, an example I think as in order here. We are going to look at a 55-year-old white woman and the question is, at what 10-year hip fracture probability is it cost-effective to treat?

And we are going to take the case of treatment costing $600 per year because that is comparable with what the cost of the intervention used in other analyses, and we find an absolute risk of 3.1%. Well, without a prior fracture, does her risk exceed this? No, it doesn’t.
Well, if she has had a prior fracture...does her risk...and no BMD, does it exceed it? No. What if she is a smoker? Well, yes, then it does exceed it. What if she has a family history of fractures? Yes. It will be cost-effective to intervene. What if she were a corticosteroid user? Yes.

And again, what if she had a BMD with a T-score below -2.5? Yes, intervention would be cost-effective. We could take the same case and if the person were slightly older, we'd find that with a prior fracture, it would indeed be cost-effective to intervene.

So in summary, constrained health care budgets do motivate the need to consider the economics of osteoporosis intervention. Absolute risk is helpful in defining cost-effective intervention thresholds. There are some variations in incidence, costs, and risk thresholds from country to country and that’s why, we are thinking it’s important to investigate this for the US. And efforts are underway to update the US case to consider absolute risk and hopefully, through careful consideration, we will be able to identify interventions that provide good value for the resources invested, thank you.

Bess Dawson-Hughes: Are there questions, microphone 3?

Yeah, John Robin, Sacramento, comment for you and like your opinion. One of the problems is the US has an uncoupling of payment for medications and treatment of hip fractures. The federal government picks up the cost with Medicare. Therefore, there is no incentive for an insurance company to pay for drugs to prevent fractures.

Yeah that’s a very...it’s a good point that you bring out and that’s why I think if all osteoporosis care would benefit from more of a societal perspective where we are not thinking about who pays and who benefits from the payment. It is not hard to construct a case using the formal quantitative framework of cost-effectiveness analysis and show that from someone who is paying for the drug, in a woman at high risk from age 55 to 65, they see very little gain whereas looking at the same thing from Medicare perspective might even be cost saving. That is definitely a problem and I don’t know that we have a solution to it, but it’s important to point that out.
Bess Dawson-Hughes: All right, microphone 1? Go ahead.

John Eisman: This is...you got to put it microphone 3. It’s John Eisman. Thank you John. John Eisman from Sydney. I guess one of the things that concerns me is for many of these sorts of analyses there is a very intense focus initially on hip fracture, probably for two reasons.

One is that they are most expensive and two, they are the one that are easiest to track through most medical systems, the most...the ones that are best followed. But there are lot of other fractures that do occur, that generally tend to get ignored. They have costs; they have impacts on quality of life that people understand, as I look at them more closely. I am just worried whether this relatively narrow focus on some of the quite big few really underestimate and contribute to the under treatment, which is a major problem I think.

Anna Tosteson: Well, thank you for that comment and I think I should clarify that although we show the 10-year risk in terms of hip fracture in all of these economic analyses, the value of preventing the other fractures, both in terms of cost savings as well as in terms of quality benefit are actually fully integrated into those models. We are just choosing to communicate the absolute risk using hip fracture, but the other fractures actually are included in these analyses.

Bess Dawson-Hughes: Front microphone.

Joan McGowan: Joan McGowan, Bethesda. I think that I understand and you understand that speaking to policymakers, you need this kind of economic analysis and that we need to have this as background. But I really think you need to marry that with being able to talk to practicing physicians and the consumers of these treatments, by using some of the information from Dr. Melton’s talk to motivate, not only that this will only help you this much and if you are at low risk you are unlikely to benefit, but also bringing in the risks. We know that every intervention has a risk and I think seeing
this in isolation, it’s a little bit worrisome that it won’t be as welcome by the practicing physician communities who say, but my patient is worth it. I will do anything for my patient and as a person I don’t care how expensive the drug is. If you can save me, save me.

You need to marry the two approaches to...yes, that is to the policymakers but to practicing physicians, it isn’t worth it to you. If you are at low risk, you are at more risk of side effect than you are of benefit.

Anna Tosteson: Yeah, I think that’s a very important comment and one that really gets at something that we care a lot about at Dartmouth, which has to do with patient preferences and informed decision making and sorting out risks and benefits. I think that the movement towards absolute risk to communicate with patients is very exciting because I think it will give an opportunity to communicate with people about what the risks are in an open way and I am using some of the methods that Dr. Melton showed that his colleagues have been using. We can begin to understand and maybe help people begin to explore what’s important to them. I think that we will always have...there often is a little bit of a tension between kind of the policy statement, but we can’t support this treatment because it’s not cost-effective in individual decision making. But my hope would be that the cost-effectiveness analysis can provide some rational kind of broad guidelines but not very specific for each individual patient. I think at the individual patient level, it will always come down to their individual risks and preferences.

Female Speaker 2: Sort of just continuing from what Joan said and from the woman that was concerned before about the 50 to 65-year-old, my concern is about prevention and the individual patient that I see that has the bone densities done in her 50s or 60s and wants to prevent it. I don’t understand where this absolute fracture risk, where prevention is in all this. I don’t see it. Maybe I am not mathematically oriented, but I haven’t quite figured out where that falls in on this.

Anna Tosteson: Well, this might be an opportune moment to invite the other speakers to come in and...
Bess Dawson-Hughes: If we could save your question for the panel...

Stuart L. Sliverman: Yeah, it would be a panel question.

Female Speaker 2: Thank you very much.

Bess Dawson-Hughes: I want to make a couple of comments that relate to these last few questions from the US perspective, where do we go from here? Well, what we had planned on the part of the NOF was to have a technical publication that will contain a lot of the information that you heard today and more concerning other fracture sites.

We will also then develop a translation of that that will be a user-friendly guide for physicians, in other words, a completely revamped NOF physician’s guide. We have a committee in place now that consists of members of the National Osteoporosis Foundation, The American Society of Bone and Mineral Research and the ISCD, the International Society of Clinical Densitometry, who will develop a draft that will include a great deal of information and emphasis on prevention. We will also address, who at this point should get a bone density and what recommendations would you make in terms of treatment?

This guide, as the previous guide, is not intended to restrict care and it’s not intended to replace clinical judgment and patient preferences and patient values. It is meant to illustrate a benchmark that many, particularly busy primary care physicians will be able to use.

It should be user friendly and clearly laid out. So that’s where we are trying to go. When we have a draft of this document, we will review it, have it reviewed by the three societies I just mentioned and in addition, by the Interspecialty Medical Council.

This is a group that is assembled by the National Osteoporosis Foundation, consists of 22 professional organizations over 800,000 physicians to get their input in how this works for their specific applications, that would be orthopedics, it would be Rheumatology, Endocrinology, The American Medical Association, etc.

Once we get a version that will be as acceptable as possible for this group, it will then go out for use by primary care physicians and others. So we are not going to stop with the technical document and keep our physicians and ourselves and our patients wondering, now what?
Ultimately, we hope that these absolute fracture risk values will appear on the DXA printouts, which will bring them right onto the desks of the primary care physicians and then able this activity to go forward. So, with that, I would like then to reopen the session for questions. Yeah.

Male Speaker 4: Who has got the questions?


Male Speaker 4: Can I just follow on to Joan McGowan’s concerns, because I saw some heads nodding in the back? There was a cost-effectiveness analysis underlying the current NOF practice guidelines.

This is not different in any way. And what was done there, those guidelines were based on clinical judgment. What makes sense to clinicians, what do we...what patients do we think are to be treated and not be treated and the cost-effectiveness analysis was just designed to try to buttress what seemed clinically reasonable.

It wasn’t a situation where the cost-effectiveness analysis tells clinicians that they cannot do something that they think makes clinical sense. And so the cost-effectiveness analysis would be used exactly the same way here. Can we justify to payors the things that we are recommending on the basis of clinical sensibility and, so I don’t think you have to worry that clinicians will be twisted around by the economists here. This guideline will make clinical sense and my guess is it won’t be enormously different from the one we have today.

Stuart L. Silverman: Shall we go back to the question, maybe John, you can help us a little bit, as our audience seems to be concerned about the issue of whether we are actually addressing prevention or not?

John A. Kanis: Let’s assume for the sake of argument that we are addressing treatment, because most scenarios...

Male Speaker 4: I can’t hear.
John A. Kanis: I can’t shout any louder. Is that better?

Male Speaker 4: Yeah.

John A. Kanis: Let’s assume just for the sake of argument that we are handling treatment, okay? So, let’s turn this into a prevention argument. You can’t prevent in all patients and that comes down to the kind of global strategies. One is because we don’t have global strategies that have been tested.

The second is that drugs and interventions are expensive, so we can’t give everybody bisphosphonates or whatever in the water. And thirdly, because they have side effects. So we have to target those at higher risk. And this is a way of accurately or perfectly or more accurately than is hitherto possible with the use of BMD alone to assess fracture probability and therefore to prevent fractures in those at highest risk. Now, it’s up to the clinician or health economists or national policies to say at what level of that risk is a treatment intervention threshold.

But here I think that you have the tools, a greater platform technology that you can assess risk and intervention thresholds exactly for prevention in a better way than you could control. The other comment I just make from what Joe and Joan were saying is that the guidelines shouldn’t be dictated by health economics, but of course they should be justified. And I think the other area that osteoporosis suffers from is that we have to make osteoporosis competitive with other chronic diseases. And hypertension and hyperlipidemia would be good examples, and so we should be focusing not only on the health economics of osteoporosis but how that interacts with other chronic non-communicable diseases that are important to developed societies.

Stuart L. Silverman: Microphone 1 please.

Male Speaker 5: Yes, thank you, (inaudible) from Brazil. As Dr. John Kanis, I also live in the underdeveloping country and we are very afraid about the issue of willingness to pay just because it’s very political.
And you know, we...I want just to ask you if there is a number, a minimal level of ethical gross line that defines people for our countries, which level of absolute risk we should address to treat, just because our gross internal project per capita is perhaps 15% of the US and so...?

John A. Kanis: There is no answer to that question, and if there was an answer, I wouldn’t certainly...wouldn’t want to give it for Brazil.

But I think it’s a generalization for developed countries and some developing countries, for example in Europe, about two to three times GDP is a kind of cost-effectiveness threshold that seems to work. Nice guidelines give £20,000 to £30,000 which is $30,000 to $50,000 and that’s about twice the GDP.

Same kind of threshold as Anna was mentioning, the same kind of thresholds that are used in Sweden. So it’s that kind of thing, but in developing countries, I think the equations are different because as you know the probability of practice is also low and you have other healthcare priorities.

Stuart L. Silverman: Okay, microphone 4 please?

Male Speaker 6: This is a longstanding developing problem we have had over the last 15 years of cost-effectiveness arguments. And I think that...what we want to understand is who we are talking to and it has been brought up several times that what we are talking to here is we are trying to figure out as physicians.

We should remember that we are physicians. We are talking to payors and what we are trying to do is learn the language that payors speak, which is this stratified risk actuarial analysis and that’s what they understand and they hear. When we try to talk to the patients, they want to know how much we understand about them.

Risk in actuarial terms is a way to hide the fact that you don’t understand and I think the patients are recognizing that when we talk to them about risk, that we are not talking to them about them as individuals. We do not understand what is actually going to happen to them and why it might happen and how our interventions work or the categories of disease, which is the real issue. Our categories are so heterogeneous that the risk is applied because we do not know how to apply the treatments appropriately to truly prevent with understanding. We need to be able to take both approaches.
We need to be able to talk to the payors about where we are now, but we also have to recognize it as physicians. It’s our responsibility to clarify that confusion by re-developing our analysis of disease that we understand the true process and understand the nature of the intervention, so that we can intervene appropriately.

If we do that, all the costs come down, everybody wins.

John A. Kanis: Thank you.

Joseph Melton: Yeah. I think everybody would agree with what you are saying.

Stuart L. Silverman: Yeah, microphone 3 please.

John: Hi, I am John (inaudible). I applaud your efforts. I think this is sorely needed. I think there is probably...we all are aware that there are patients who are over treated and patients who are under treated. My concern was and I guess the question is...I assume that if the models for making a decision about intervention assume that the intervention is equally effective at reducing fracture risk from each of the risk factors that go in to the equations. So, I guess the question is do we know that the drugs that we have, the treatment options that we have are equally effective at reducing fracture risk from the additional risk that comes from the age, from smoking, from genetics, etc., etc., because most of the therapies tend to be for strict bone biology, bone density kind of parameters.

John A. Kanis: Yeah, a good point. And the answer to that is yes in so far as we can determine. And as I was mentioning earlier, the level of evidence that we can look at is not the highest level of evidence, but an intermediate one. But it’s true to say that the risk factors have been looked at for the bisphosphonates, for raloxifene and the SERMS and PTH and for Strontium. And for those treatment modalities, the risk factor...they validate the use of these particular risk factors.
That doesn’t mean to say that it would necessarily apply to new products.

John: Great, thanks.

Stuart L. Silverman: Yeah, our last question.

Robert Downs: Bob Downs, Richmond, Virginia. There are confidence intervals around these estimates and I wonder if each of you would discuss how actually considering those confidence limits and the degradation of what that does to the actual estimate of absolute fracture risk has an impact on the model, the prediction of cost and how it might be used in practice by clinicians.

John A. Kanis: I am not sure I had all the question, but though I had the beginning part of the question, which is the question of confidence levels.

You could put confidence levels on this if you wish, but I think its kind of inappropriate. The better way to look at is, what is the performance characteristics of the tests that you are applying, how good is the test? And the test is not perfect, but let’s use RAC curves or gradient of risk is probably the best.

And for the prediction of... with BMD of any osteoporotic fracture, the gradient of risk is about 1.5. The use of this algorithm with BMD gives a gradient of risk that is about double that.

Joseph Melton: Let me just add to that. When you have any kind of disease versus modeling, you put confidence intervals around all the pieces and then the confidence around the resulting model, there is nothing that works. We are talking about the Gale model for breast cancer, from here to there, Framingham model of heart disease. So you wouldn’t have confidence on any predicting model, not to mention your clinical judgment, if people put confidence intervals around that.

And so, we are doing the best we can here and we are in better shape than any other disease because our dataset is actually more robust than the ones that are currently being used to manage cancer patients and heart disease patients right this minute.
Stuart L. Silverman: I think we have a high confidence interval at least confident. But this was a very good symposium and I...on behalf of myself and Bess Dawson-Hughes, our co-chair and behalf of our three speakers, Dr. Tosteson, Kanis and Melton, thank you all for attending.