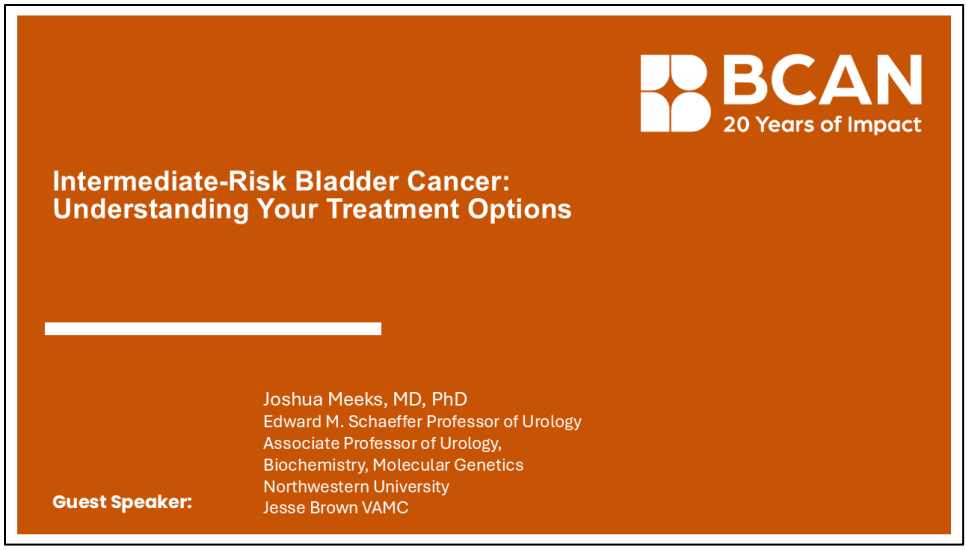


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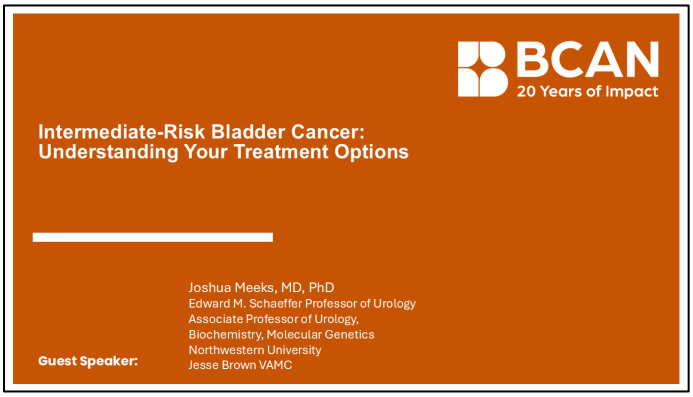
### Stephanie Chisolm:




Today's webinar is Intermediate Risk Bladder Cancer: Understanding Your Treatment Options. Navigating a diagnosis of bladder cancer can be really overwhelming. Non-muscle-invasive is just as overwhelming as muscle-invasive, and there's so many unknowns. When I started at the Bladder Cancer Advocacy Network 10 years ago, you were either diagnosed with low-risk non-muscle-invasive bladder cancer or high-risk. Nobody talked about intermediate risk.

So today, BCAN is delighted to welcome you to an engaging and informative webinar with Dr. Joshua Meeks, a urologic oncologist and scientist at Northwestern University in Chicago. Dr. Meeks has almost 20 years of experience in the diagnosis, treatment, and management of bladder cancer and has completed many, many, many research projects specifically focused on bladder cancer. He received his medical and PhD degrees from Northwestern University in 2005 and completed a urology residency at Northwestern in 2011, a urologic oncology fellowship at Memorial Sloan Kettering in New York in 2012.

He'll provide a comprehensive overview of treatment options specifically tailored for patients with intermediate-risk, non-muscle-invasive bladder cancer. So remember to add your questions to the Q&A box at the bottom as you think of them, and we'll answer them at the end. Dr. Meeks, I'm going to turn it over to you, and I'm looking forward to your presentation.

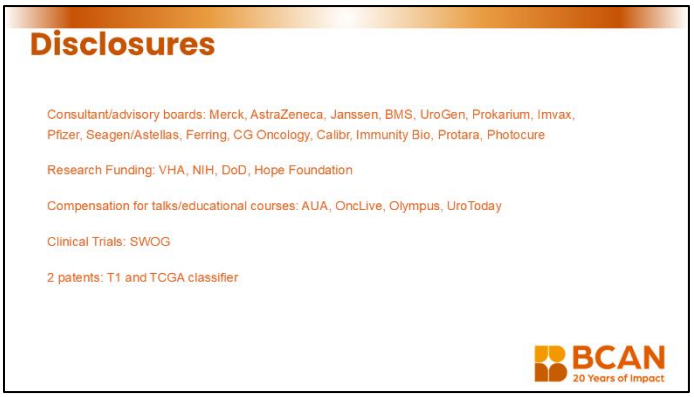
### Dr. Joshua Meeks:

I was really excited that you asked me to do this, because I agree with you totally that the whole group of ... We call it intermediate risk bladder cancers, and the first thing we're going to do is talk about what that actually is. But it's such a patient-driven concept. I have a lot of folks I care for here in Chicago that

are intermediate risk. The great point you made is that for each of our patients, that cancer is the most critical thing in their life, and it's not fair to do a comparison of life-threatening or non-life-threatening. When I'm with somebody, and we're talking about where they are in their journey, this is the most critical thing to them. What I'm excited about is that there's so much coming on the horizon for this group of folks, where I'll tell you, five years ago, I had very little to offer them. So again, I think this is a really exciting space, and I'm so happy that we're addressing this today.

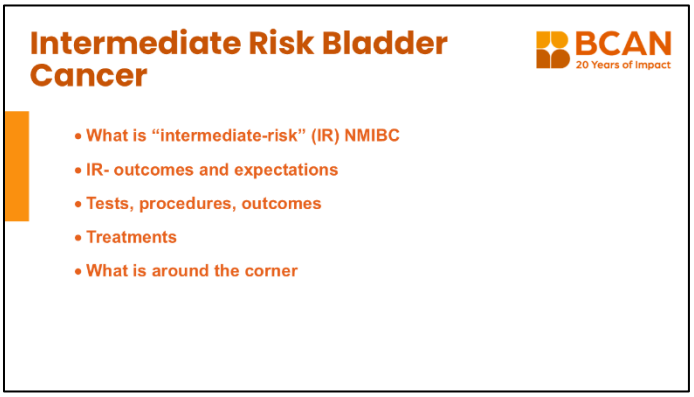
### Dr. Joshua Meeks:

Here are my disclosures, and again, I think much of this has to do with trials that we're going to be talking about, because ... I think, again, it calls attention to the fact that our partners in pharma are interested in this space, because a lot of this involves intermediate risk.




### Dr. Joshua Meeks:

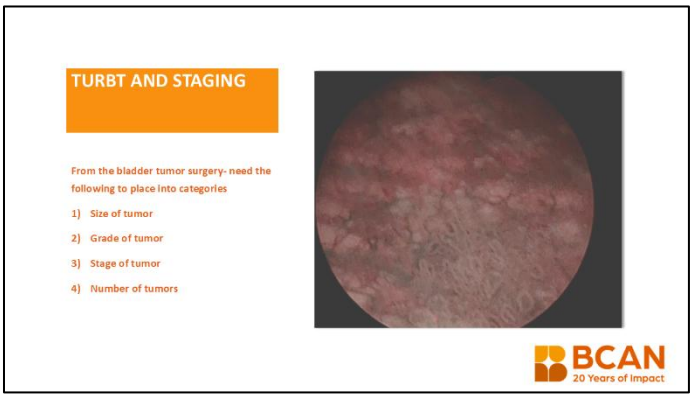
So I'm going to talk today about intermediate risk, how we define that, and then, what are our outcomes and expectations for patients with intermediate risk? We're going to talk about how I approach them and what the standard of care is, and then we're going to talk about treatments. I think the exciting part's at the end, because again, there's a lot more in the space that's developing.




### Dr. Joshua Meeks:

All right. So intermediate risk and how we define that.

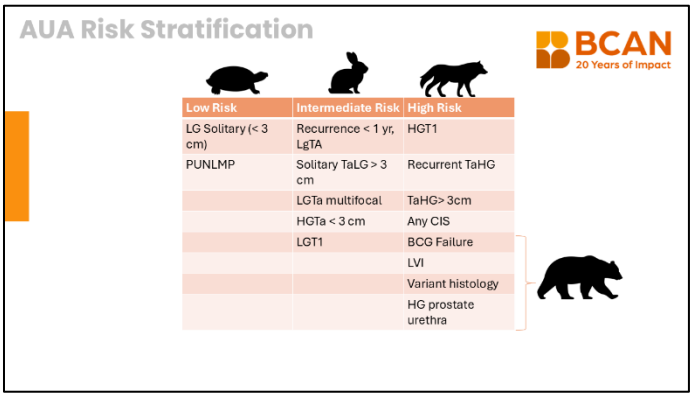
### Dr. Joshua Meeks:




So first question people ask is, "What actually is this?" And so to put a tumor in intermediate risk or to say that a patient is intermediate risk, we need information from the TURBT. So what you're seeing is a video of what a TURBT looks like. This is the surgery itself. And so as we're doing the surgery, the clinician needs not only the pathology, that will come, but also, in general, recording the size of the tumor and the number of tumors. That's what we get from the surgery. So the surgeon, as ... If you ever read an operative report, that information is usually described there. Then, that's combined with the pathology report, and together, we're able to establish a risk classification.

So this is often hard, because when, usually, I meet somebody, they want to know, "What's the next steps after surgery?" But really, we can't do that until after the surgery's done. We know what things look like at surgery, and then we get the pathology report. So putting all that together, we're able to come up with a risk status.

### Dr. Joshua Meeks:



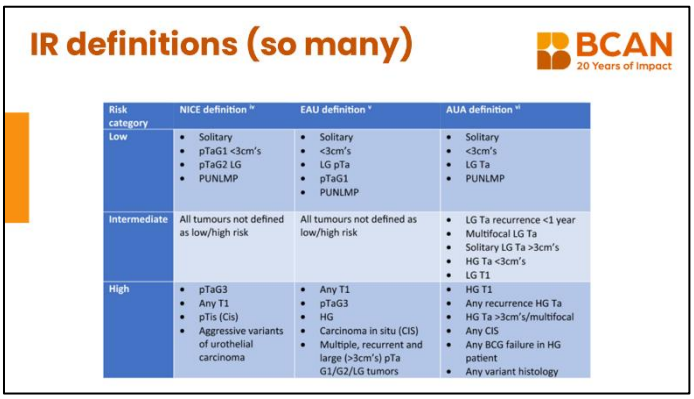

And so there's really basically three risk status that people use. This is from the AUA because we're urologists in the US, so it's the American Urologic Association. Really, the AUA has set up three groups, and I kind of lump these into four major characters here.

So the turtles of bladder cancer are the low-risk tumors, and generally, they're pretty slow-growing. That's why we call them the turtles. They're low-grade tumors, single tumors under three centimeters, so very small. I think this intermediate-risk group we'll talk about is bigger low-grade tumors, tumors that come back within a year, multifocal, meaning they're in more than one area. In the US, we say that a high-grade tumor under three centimeters is considered intermediate risk, and then the high risk is everything else. Those are much more like ... I would consider them sort of the wolves of bladder cancer in that they tend to be more aggressive. You have to worry about them more.

Then, there's sort of the bears that are kind of the apex predator of bladder cancer that I worry about a ton. Again, we're not talking about those today, but that's more patients ... tumors with lymphovascular invasions and variant histology. But again, today, we're talking about those, the rabbits or the intermediate risk.

**Dr. Joshua Meeks:**

Now, this is very clinical. This is just to show you that there are three different kinds of classifications, and I kind of wanted to spend a second on that.




**Dr. Joshua Meeks:**

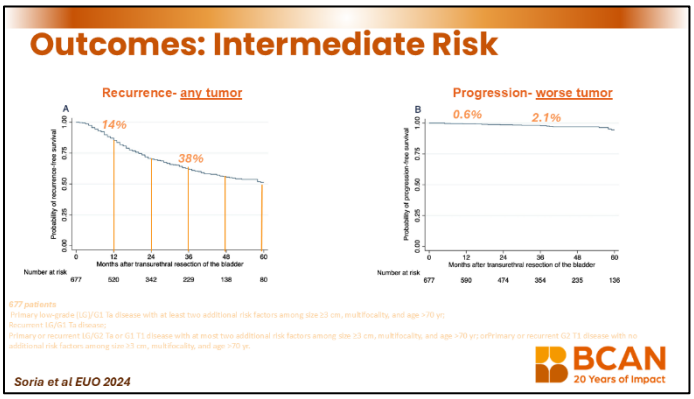
And so to hit the easy button and to say, "How do other people around the world think about this?" they basically say, "Okay. There's low-risk patients." So Stephanie kind of talked about those. Those are low-grade small tumors, individual, single ones. That's low-risk. High-risk is anything high-grade, anything Stage I, anything with carcinoma in situ. That's all high-risk.


Then, intermediate is everything else. So it's a big group of patients, and I think there's a lot of value to this even though we don't use this specifically in the US. But I think that kind of fits this group. So basically, we're talking about recurrent or multifocal low-grade cancers that keep coming back. When I think about these, these are usually patients that I work with that are extremely frustrated by their cancer, that, again, even though it's not life-threatening, these are cancers that keep coming back, and we just don't have a great solution for them. So again, recurrent or multifocal low-grade cancers. Okay?

**Dr. Joshua Meeks:**

And so what do we expect? We talk about recurrence, and so I kind of want to be very clear about our outcomes here.

### Dr. Joshua Meeks:

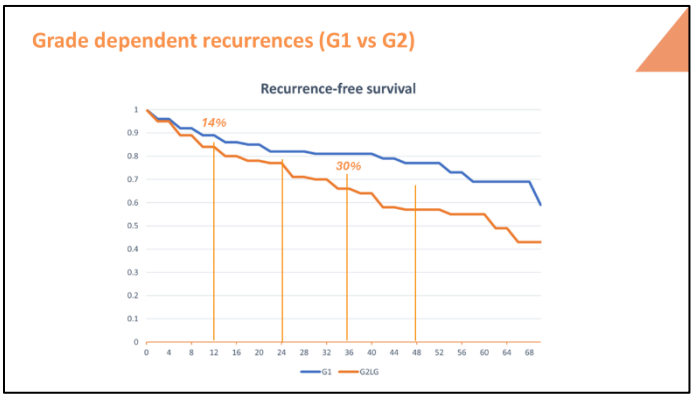



So we have recurrence, which means a tumor coming back at all. Most of the time, it's going to be those same low-grade cancers. That's a recurrence. Progression is when things are getting worse. So that's usually either a high-grade tumor or an invasive cancer, but that's a more concerning outcome. So when you look at these outcomes, that's a Kaplan-Meier curve, and so if we start off with a 100% of patients, that's when they start after surgery, you can see that by a year, about 14% of those patients will have had a recurrence. This is without therapy.

By three years, over 38% have had a recurrence. And so in general, by the time you get out to about five years, it looks like about half of patients have had some form of recurrence. Now, that's most of the endpoints that we're worried about for intermediate-risk bladder cancer. It's the tumor coming back. And so I think the first thing I try to talk to folks about is this is often not a cancer that I don't anticipate it's going to take your life. So if you look at progression, by five years, the risk of that is about 2%. So folks are very unlikely to die of this cancer, but it doesn't mean there's a significant burden of recurrence.

So recurrence in these cancers are, again, about 50% at five years. So it is a cancer that will come back, and that's where our strategies are really aimed towards decreasing the risk of tumor recurrence. Again, progression, luckily, is a relatively rare phenomenon, and that certainly can happen. But really, what we're trying to do is keep people cancer-free. And so that's the endpoint that matters the most in this field. Does that make sense? I think that's a critical thing for this cancer, is this cancer is about getting good, long disease-free intervals, and obviously, cure in this case means cancer not coming back.

### Dr. Joshua Meeks:

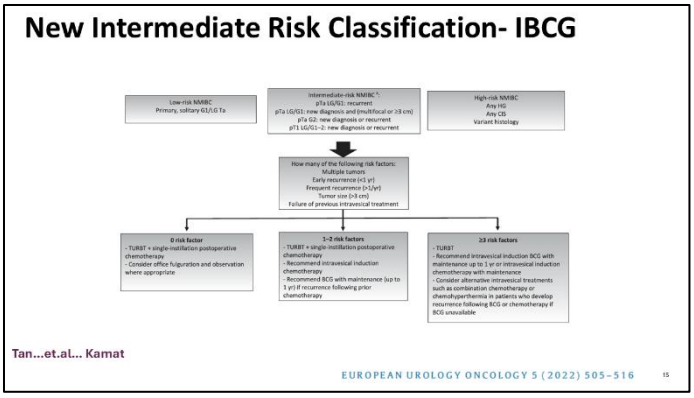



Now, a lot of that comes down to some of the challenges in this group of patients, because it is a pretty heterogeneous cancer, meaning that there's a lot of variability. So in this line, again, we're starting with a hundred percent of patients starting at time zero, and by the time we get out to five years or 60 months, there's a big split there. The difference in these two lines is grade. So we kind of have gotten rid of grade 1, 2, 3, but this is an older system, where it's Grade 1 versus Grade 2. You can see that by going up to Grade 2, the rate of recurrence is significantly higher. So again, that kind of goes back to some of the variability in this group of patients.

### Dr. Joshua Meeks:


Now, I think the big challenge for us as providers and what we try and talk to our patients about is that there's a wide spectrum of cancers in this space. So how do you individualize that to get to kind of a Goldilocks point, where you're not overtreating everybody? Because you could treat everybody and give them the most amount of therapy, but you're probably providing a lot of treatment that people don't need and making people feel worse. Alternatively, there's a lot of people who are going to recur, and some of them will progress. So is there any way to tailor that where we're coming to every patient and saying, "What matters the most to you, and what are the endpoints that matter to you? How do we make this individualized?"

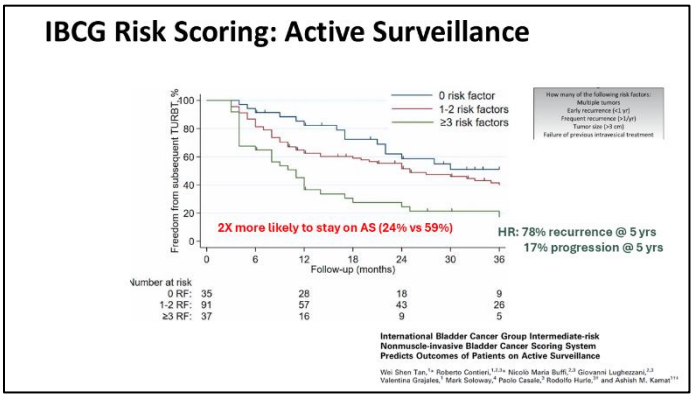
### Dr. Joshua Meeks:




That's kind of where we've tried to evolve as providers for our patients. Again, I credit Dr. Kamat and the IBCG for this classification, because basically, if you look at all the possible tumors that are involved in this group, we've tried to set up, or he's tried to set up a point system in order to put people into zero, one to two, or more than three risk factors. And so when I'm trying to talk to a patient about where they fit, we sort of go back to this almost every time, and I'm going to kind of do a summary at the end.

But here are the factors that we think matter. So are there multiple cancers, meaning in different parts of the bladder affected? Have they had an early recurrence, meaning that within the first year, have they had more than one recurrence? Are they having frequent recurrences, so more than one tumor a year? Is the size of the tumor bigger than three centimeters? Have we previously treated them with something, and they've not had a complete response? So each one of those is considered a point or a risk factor, and then, based on that, we can sort of put people into no risk factors, one to two, or more than three. This is actually a pretty straightforward system to do, and again, I don't think this is information that you would say, "Oh. Well, you're a three. You should do this." But I try to ... As you'll see coming forward, this really helps to put people into different risk groups and really provides information about what we anticipate the next year is going to look like.

### Dr. Joshua Meeks:




So again, we have three risk groups, and this is kind of how those risk groups pan out. Again, these are Kaplan-Meier curves, so we start off at a hundred percent, where everybody's doing great. Then, we start to have events. And so you can see that the blue line, the line on top, they're having fewer events, and then the green line, that's the folks with more than three risk factors. They're having more events. And so if you look at the outcomes, that if you have more than three risk factors, you're more than twofold likely to have an event. And so again, at five years, for high risk patients in this dataset, it's almost 80% of people have had a recurrence, and up to 17% have had progression.

So again, I think this is an important thing as far as counseling and thinking about where people are and why we, for example, want to escalate some versus others. Again, it provides some reasoning for that. I think that's an important part. Stephanie, is that clear? Do you think that makes a lot of sense, and do you have any thoughts about this?

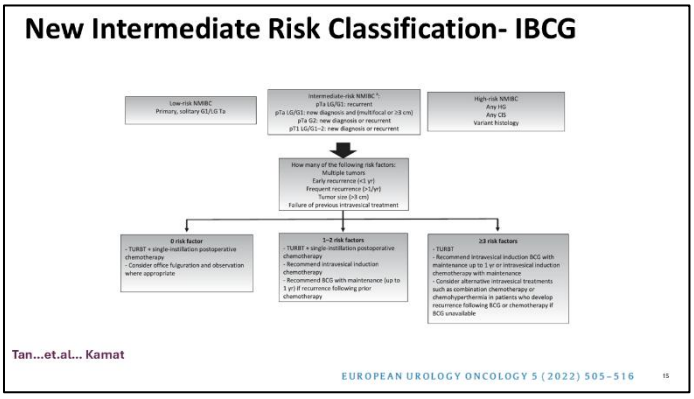
### Stephanie Chisolm:

I do think that makes sense. I have a question. You mentioned something about recurrence, early recurrence is within a year. So what about those people that have a new tumor every 18 months? If they're consistently doing that, is that another thing that should be counted?

### Dr. Joshua Meeks:

Yeah. That's an interesting group. I have a discussion with folks, because it is always like, "Well, you're just over 12 months, and so you're not ... technically don't meet the definition of intermediate risk." I actually think they may be a little different, and I don't really know where to have that discussion. In general, if you look back to our point system here, they wouldn't really get any points from that. So they kind of would be in zero.

### Dr. Joshua Meeks:




### Dr. Joshua Meeks:

And so if you look for the zero point group folks, they get the single installation, and you follow them.

I tend to think if you can make it more than 12 months, which, again, would be two cystoscopies with no recurrence, in general, those folks usually do pretty well. I tend to, personally, at least, I tend to offer them more just like the fulguration in the office and would really probably not escalate them to treatment unless they said, "I just

can't deal with this." So technically, if it's a little bit more than a year, they're probably doing well, and in general, I try and do less is more in them.

### Stephanie Chisolm:

Okay. But if they did say, "I love you. I love seeing you, but I hate coming in here and having this procedure every other year. Is this something we can do something a little more substantial to keep the cancer from coming back?" is that where perhaps they could be offered one of the treatments that you're going to discuss a little bit later?

### Dr. Joshua Meeks:

Oh. Yeah. Absolutely, Stephanie. So you could offer them intravesical therapy. I think the concern for that, though, is once you get to ... We don't really have a way to individualize that where they're not getting a year of treatment. So generally, we'll talk in a bit about our treatment regimens that we offer for intermediate risk, and that's, in general, about 15 doses. So when you compare a scope and office-based fulguration, which would happen maybe once a year or once every 15 to 18 months, I think the burden of that is much less than coming in for 15 doses of therapy over the course of a year, so especially if people don't tolerate it.

So I usually really try to deescalate, but if they wanted therapy, I'd say, "Well, why don't we just do six, and see how you feel, and see how it works." I think one of the things that we'll talk about is the chemotherapy, while we're making decisions to escalate to chemotherapy, not only is it not a free ride, but it's also not been the most effective. It's not like we're offering people going from a 30% recurrence rate to zero. With the best therapies we have, one of the challenges of these tumors is that, and this is kind of, again, where my scientist cap goes on, they're not that much different than the normal bladder lining.

So a lot of the therapies that we've developed, and the reason, for example, that you talk about high-grade and high-risk is that our therapies work better in those cancers, because the tumor has different biology than the normal bladder lining. Many of these tumors, biologically, are pretty similar. So I think some of the challenges is finding the best therapies for them. Now, if we have therapies that are very, very effective with less toxicity in the future, that may really change how we look at this.

### Stephanie Chisolm:

Yeah. I don't know that anybody's got to that point yet where there's less toxicity in terms of potential for side effects or irritations and things. So okay.

### Dr. Joshua Meeks:

Well, we'll get there.

### Stephanie Chisolm:

Good points. Good points. Yeah.

### Dr. Joshua Meeks:

I think there may be some we'll get to at the end that are maybe pretty close.

### Stephanie Chisolm:

Okay. Good.

### Dr. Joshua Meeks:

All right. So I just wanted to mention this. So again, this is the number of risk factors as columns and then the chances of having progression, and again, the only point I'm making with this is as the number of risk factors go up, the risk of progression gets higher. So again, those are significantly different, suggesting that the classification is helpful, and it's important to talk to people about what they expect.