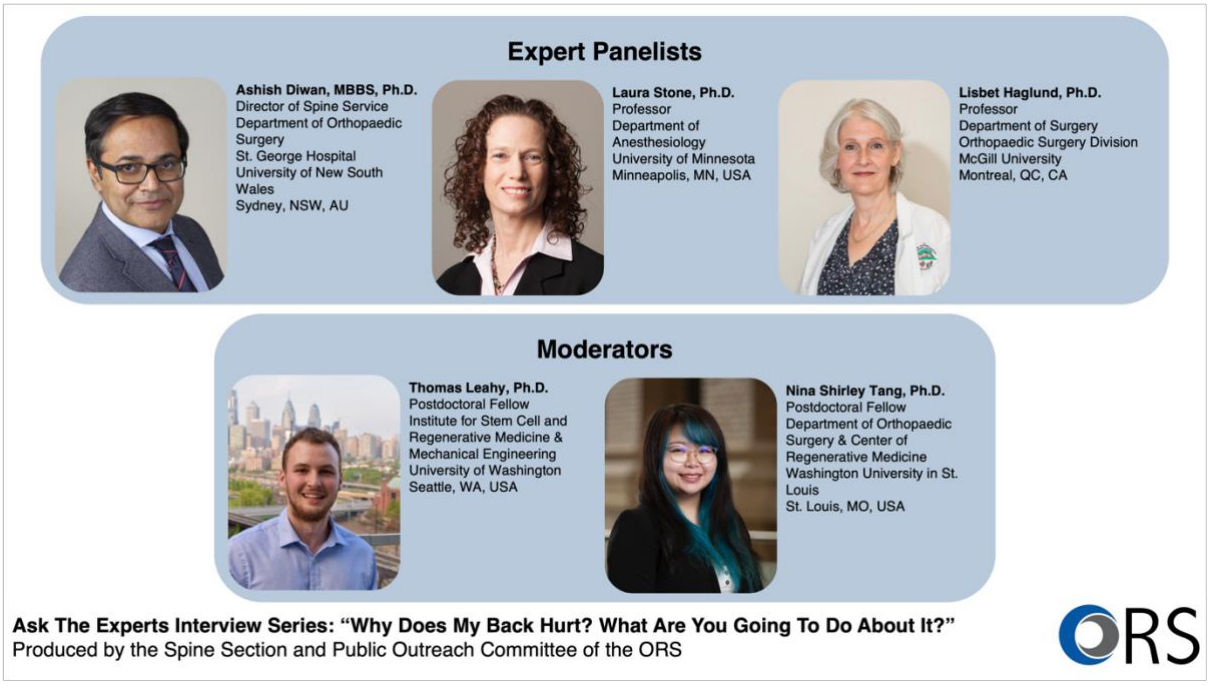

Thomas Leahy, Ph.D. Hello everyone and welcome to the next installment of the ORS Ask the Expert Interview Series. Today we'll be focusing specifically on the Spine Section and the title of this video is "Why does my lower back hurt? And what are you going to do about it?"

For those unfamiliar with the ORS Ask the Expert Interview Series, the primary goal of this interview series is to leverage basic science and clinical perspectives and expertise to address challenging and or timely topics within the field of orthopedics, research, and medicine. Ultimately, our goal is to provide information to the general public in an accessible manner. And this is the third installment of the ORS Ask the Expert Interview series.

I'll begin by first introducing myself. My name is Thomas Leahy. I'm a postdoctoral fellow at the Institute for Stem Cell and Regenerative Medicine at the University of Washington in Seattle. I did my Ph. D. with Louis Soslowsky at the University of Pennsylvania, so I have a deep fondness for tendons and orthopedics and I'm continuing my education here in Seattle.

I am a member of the ORS Public Outreach Committee, which is the ORS committee that runs the Ask the Expert Interview Series. I'm excited for this next installment. With that, I'll turn the floor over to my co-moderator, Dr. Tang, to introduce herself.

Nina Tang, Ph.D. Hi, I'm Nina Tang. I'm currently a postdoctoral fellow in Dr. Farsh Guilak's Lab at the Center for Regenerative Medicine and Orthopedic Surgery at Washington University in St. Louis and I currently focus on obesity and how it drives orthopedic joint diseases on the epigenetic level. My PhD was at The Ohio State University with Dr. Davina Purmessur in the spine and how we can use non-viral methods to reprogram disease cells in the intervertebral disc of the spine. I'm also a member of the Spine Section Membership Committee for ORS, and I'm very excited to be here and co-moderate this session.

So, with that, I will introduce Dr. Ashish Diwan, one of our speakers for today. Dr. Diwan is a surgeon-scientist and currently is director of spine labs and spine service at the St. George Hospital campus of the University of New South Wales in Sydney, Australia. Following his

orthopedic training and PhD, he completed a ACGMD fellowship in spine and scoliosis surgery at the Hospital for Special Surgery in New York. And he was the Philip D. Wilson awardee for his work on BMP2 and interior body fusion. This was critical work leading to the eventual FDA approval of infuse. On his return to Australia, he established his research group and has since then graduated 10 PhDs and a number of orthopedic surgical fellows, who have gone on to academic leadership positions. And he has focused his innovation on bench to bedside approaches. And is named inventor of 20 patents and helped with two university spin-outs. His focus has been predominantly in 'gap-in-treatment' areas rather than iterations to existing tools of the trade. The challenges of translations, especially in the context of complexity of pain is where he wishes to focus the next part of his innovation journey.

Thomas Leahy, Ph.D. Our next speaker is Dr. Laura Stone, who is a professor in the Department of Anesthesiology at the University of Minnesota. Dr. Stone received her PhD in neuroscience at the University of Minnesota and training as a postdoctoral trainee at the Oregon Health and Sciences University. She's the first recipient of the John Bonica Postdoctoral Training Fellowship from the International Association for the Study of Pain. After working in both biotechnology and academia, she joined the faculty at McGill University in 2007, where she co-founded and directed the Quebec Back Pain Consortium. She then returned to the University of Minnesota in 2020. Dr. Stone is an inventor on 7 patents, has received funding from both the NIH and the Canadian Institutes for Health Research, has co-authored over 80 manuscripts, and was awarded the Early Career Award from the American Pain Society. Current research projects in her lab utilize both pre-clinical models and patient populations to investigate the mechanisms underlying low back and musculoskeletal pain, the optimization of pharmacological and non-pharmacological treatments, and the epigenetic regulation of chronic pain.

Nina Tang, Ph.D. Dr. Lisbet Haglund is a basic scientist and a tenured professor in the Department of Surgery, Division of Orthopedic Surgery at McGill University in Montreal, Canada. And Dr. Haglund has a strong interest in musculoskeletal research spanning from tissue injury, degeneration, and inflammation to regenerative medicine. And she has been active actively involved in bone cartilage and intervertebral disc research throughout her career. She has developed a research program aiming to enhance understanding of the molecular mechanisms leading to pain in spine pathology and more precisely to develop molecular markers to follow disease state, progression, or effect of treatment. And most importantly to develop novel therapeutic interventions for painful spine conditions. Dr. Haglund is a member of the Miguel Scoliosis and Spine Group, and she's working closely with a clinician team, which has allowed her to generate an extensive cell and tissue bank of both symptomatic and non-symptomatic cells and tissues. Her research program is currently funded through the Canadian Institute for Health Research (CIHR), the Shriners Hospital for Children, and the Arthritis Society.

Thomas Leahy, Ph.D. So, with that, I think we will begin the official interview section. As I mentioned, the goal of this series is to provide information in an accessible manner to the general public. And so I thought it might be best to first start off with some definitions. And so that would be our first question, which is what is lower back pain and specifically what populations does this problem effect? And what are the most common injuries or pathologies involved in this disease?

Laura Stone, Ph.D. Let's throw that one to our clinician.

Thomas Leahy, Ph.D. That seems fitting!

Ashish Diwan, MBBS, Ph.D. Thank you for putting it up front. There are numerous definitions. One of the definitions is that low back pain is defined as a painful area in the lower part of a person's back up to the gluteal folds. So that is one definition in terms of location. That is classically what we call as lower back. Now, this may be associated with leg pain when the leg pain goes at the back of the thigh up to the calf. And that pain may or may not be associated with tingling numbness. And it is kind of important to differentiate between the two because in one set, we do not expect a lot of pressure on neural tissue elements, whereas in the latter part where you have leg pain, one would expect that some of the nerves are compressed. Some people define the leg pain separately as sciatica and use a different word. But I guess what is more predominant and what is more challenging for us as both clinicians and scientists is that low back pain so for the purpose of our discussion today, if we just focus on that low back pain. I think that will be that will be more targeted and more appropriate. What is the second part of your question?

Thomas Leahy, Ph.D. The second part was what are the most common causes of this injury?

Ashish Diwan, MBBS, Ph.D. One of the most important situations from a clinician's perspective is that the first thing you do when we have a low back pain situation is we get rid of any serious issues that may be underlying, which we call as 'red flags'. And at the outset, it is important to say that that is not a common cause for pain. Red flags include tumors, fractures, or inflammatory disorders of a serious type. They form less than about 1. 5 percent of the population that one sees with back pain. The commonest cause, by far the commonest cause, is wear and tear of the intervertebral discs, of the facet joints, and some very subtle, what we call as instabilities, which we may see in the younger population due to a breach in what we call the pars interarticularis or in the older population we may see due to persistent or chronic degeneration of the disc. So, in short, the commonest cause, I would say, is wear and tear. Alternatively, we use the word osteoarthrosis for that. That is the commonest cause.

Laura Stone, Ph.D. Well, I would like to just add a little bit, which is that one of the things that makes it so difficult to treat chronic back pain: Once the symptoms start, because of this wear and tear and instability in the spine, the signals get sent into the nervous system, and the nervous system gets kind of overpowered by the input saying that there's pain. And then the nervous system starts to change, so it almost forms a memory of pain. The nervous system changes, such that now if we are able to fix the peripheral problem, like if we're able to reverse that wear and tear, we still have this problem of what people call central sensitization, where the nervous system still thinks that there's a problem. So we now have this multifaceted challenge of fixing the original cause of the pain, as well as these central nervous system consequences.

Lisbet Haglund, Ph.D. Another complicating factor with back pain is that the pain can come from so many different tissues. It can come from, from the facet joints, it can come from the musculature, it can come from disc. So, unless we can clearly define where the pain is coming from, it's very hard to treat. So, I think that's another thing that makes this feel very difficult.

Nina Tang, Ph.D. Those are all very good points. And I think that goes into our next question of what is the role of physiology in contributing to low back pain? Like what happens with, for example, the intervertebral disc? What kind of cells are involved to generate this low back pain?

Ashish Diwan, MBBS, Ph.D. I think both Laura and Lisbet have alluded to some of the physiological mechanisms. But let me just define one more parameter going back to the previous question in terms of segmentation of pain and how we understand that situation. By the time you get what we call as neuronal issues or embedding or memory or plasticity come in, we segregate them clinically into two situations: acute back pain and chronic back pain. And that definition is sort of a three month mark is generally the acceptable cutoff period that we are expecting. So, one to three weeks, possibly six weeks is acute. Then three, possibly six weeks to three months is subacute. And then it kind of becomes chronic. So that is one set categorization.

Another one is that in the past we used to think that once you have acute back pain, you know, see the biggest problem in back pain research is we are in the same situation where cancer research was in the 60s. The attitude was do not research. What's the point researching cancer? Everybody dies. The problem we have is why research back pain that well? Nobody dies. So this is where we are. So nobody's, you know, that is going to trying to understand the problem is at its minimum, to say the least. But coming back to the segmentation issue that I was talking about is the other concept we say is if you once get an episode of back pain, the likelihood that you get a second episode within the next 12 months is close to 50%. So those we categorize in a separate group of people who got flare ups, recurrent back pain. And then if the baseline pain stays, we start calling them chronic back pain. So, chronicity has a complexity involved in around it. where the whole issue of recurrence and everything comes into play.

So, once we start off understanding that, there's another dimension to understanding it, which I'm expecting Laura to talk more about later on. But I'll put it out there so that we do touch on it, is the whole concept of nociceptive versus neuropathic pain. I alluded to it a little bit when I said leg pain versus back pain. So, when there is pain around the nerve root, or there is nerve root damage, it kind of goes into the neuropathic category, and the rest gets into the nociceptive category. So, understanding clinically all those pains and where you fit in kind of becomes important to understand aspects of anatomy, physiology, management, treatment, as we build up on our conversation going forward.

So, getting back to your question, the role of anatomy and physiology: a lot. Let me tell you that, a lot. In the early stages of life, 5 percent of the world's population has a condition where we call there is a lytic pars defect. It does not become symptomatic on everybody. So, in a younger population, that may be the cause. But the commonest reason why we see, and we see changes of wear and tear and degeneration, believe it, it is not an age-related thing. 30 percent of the world's population, if you take a cross section of the MRI scan in below 25 year of age group, will show changes of what we understand as wear and tear. Already it is existent, whether it is genetic or whether it is due to how we use it is a different issue. But the role of those things gets important in back pain. And those wear and tear we see as tear in the annulus or we see as a small osteophyte. So, I think that anatomical change then impacts how biomechanically that segment is loaded or is able to do its work of movement or carry load has a significant implication in back pain.

Laura Stone, Ph.D. This seems like a good opportunity to introduce something called the biopsychosocial model for back pain. In this model, we have the biological cause, like wear and tear in the spine, as well as psychological factors. So those of you who may be listening to this who do live with back pain may have noticed that it flares up when you have a lot of stress in your life. It's very stress dependent. If you are having problems sleeping, for example, that could make it worse. And individuals who are not well supported socially, who don't have a strong social support network, tend to have more challenges with back pain. So, because it's this complex intersection of biopsychosocial factors, it also suggests that

any kind of integration should address several of these different factors. In some individuals, the biology, the intervertebral disc degeneration, for example, might be a much stronger cause, and there's less psychosocial. But in other individuals those might be really important drivers. And one of the biggest questions is how we can intervene in all three of these areas to help diminish back pain.

And in these cases that were referred to with the recurring, so it's a sort of chronic but intermittent flare ups. Those might be mitigated by addressing some of the psychosocial factors because they're all kind of integrated. I'll make one more point and then pass the floor, but one of the biggest questions in back pain research and in clinical treatment is why do some individuals who have wear and tear in their spines, experience back pain and others do not. And some of the factors that lead into this are not the biological, because the biological might be the same, but it's these psychosocial risk factors.

Lisbet Haglund, Ph.D. Okay, so I'll turn around a little bit and look into instead what is perhaps causing the pain if it's now coming from the discs. Even if it's coming from the disc, I think it can have many different reasons. If you have a herniating disc, for example, you have the immune system coming in to resolve that, which will contribute to the pain. If you have a modic change, for example, or inflammatory environment in the end plates, it's a different type of situation causing pain. Or if you have a disc degeneration where you, for example, have nerve ingrowth to the disc, that's yet another situation where you can have pain. It's clear that the cells in the discs, in all different areas of the disc, can produce these factors that generate pain. But you also then in some situations have the immune system coming in with cells that are also producing a lot of inflammatory factors. So, it's difficult to have one answer when back pain, and even if you say back pain coming from the disc, is still not one thing. And I think that's one problem in the research that we are doing. We use a model, whether it's an animal model or an in vitro model, but it will reflect a very specific situation. And then when we try to treat patients and we enroll patients in clinical trials, we mix them all together. So, until we can really stratify the patients and understand why they have back pain and which type of treatment would be beneficial for one or the other, I think we will have very hard time seeing strong effects of the new treatments that we provide. And I think that we can see that from the few systematic reviews and meta-analysis that are out there, all of them show that the biologics have very limited effect, but it's because it's this mix of all different conditions together.

Thomas Leahy: I think those were really thoughtful answers, and I think they kind of segue nicely into what I think our next question should be. So, we've kind of introduced some ideas behind nociceptive versus neuropathic back pain as well as the biopsychosocial model of kind of why a patient might be experiencing back pain. And we've just now kind of brought up ongoing research in that field. I was wondering if this question perhaps might be best directed towards Dr Stone, but kind of a state of the field in terms of the ongoing research that's going on there. It seems like a really complicated area for definitions and models, which was also just mentioned as well. So I think kind of a general public state of that research field would be really helpful.

Laura Stone, Ph.D. We could spend days on this. But, on the sort of very basic science side, there's a lot of research being done now, trying to understand the cellular changes that happen because of this wear and tear. And if we can better understand at a cellular level what's happening: why the cells are kind of responding in a way that they make all of these Inflammatory mediators that then activate pain sensing fibers and cause pain? Can we slow down or reverse that process? So that's, there's a lot of research being done at that cellular and molecular level.

At the level of the whole animal, we have an array of different animal models that we use to study both facet joint degeneration and intervertebral disc degeneration, as well as the pain that is caused by those. So, we have animal models where, in one case, maybe there's a genetic mutation that causes the discs to degenerate more rapidly. And then the animals develop signs of sciatica as well as discomfort in their lower back region. There's also larger animal models like dog models. There are some dogs who develop intervertebral disc degeneration naturally. And that's a really exciting area for study because we can then try interventions in these companion animals and have the owners help us to understand whether that animal is having less pain, and that's kind of a nice intermediate to humans. There's also pig models and sheep and other larger animal models. Some of the things that we're really interested in in the preclinical models are the cellular changes: how the degenerating tissues in the spine activate the nervous system? Can we maybe just turn off the nervous system when it gets activated by the spine? That would be a great way to treat pain. And there's also a lot of research going on in how chronic pain changes the nervous system and what can we do to slow down or prevent those changes so that it doesn't become embedded?

So, I'll give one example of work that we're doing in my group, where if you look at the treatment recommendations for back pain, one of the most common interventions for which there is the best evidence is physical activity, just increased physical activity. And I hesitate to use a word like exercise, because exercise has all these connotations of being kind of scary and painful, whereas it's really just getting up and going for a short walk might be helpful or doing some stretching. Yoga has been shown to be really helpful for back pain. So, in our lab, we have a rodent model of intervertebral disc degeneration, and we give the mice these little running wheels. So, it's just a little plastic wheel and they love them, and they just like run all the time. You go in the animal room and they're just like… [mouse running imitation]. And after a couple of months of just running when they feel like it, their pain symptoms diminish. So, they have less pain in the back region as well as less radiating pain in the legs. And, so, we're studying the mechanisms by which that's happening. And one of the really interesting things is that when joints and discs degenerate, these nerve fibers start to grow into the tissues that are normally not supposed to be there. And so these nerve fibers, once they grow into the tissues, they're going to sense changes in those tissues: movement or inflammatory mediators that are not supposed to activate the nervous system. So, you now have a situation where there's pain with just normal movement or even with no movement. So, in these mice that have their little running wheels, we found that just the act of this increased physical activity reduces this increased innervation of the discs so that they begin to look more like healthy discs that don't have this increased sensitivity.

Lisbet Haglund, Ph.D. I don't know if I can jump in here on the exercise part (let's call it physical activity). Because that's an important thing to bring up about the disc as well that it's an avascular tissue. A human lumbar disc is a big piece of tissue. It's about six centimeter in diameter and a centimeter tall, and there's no blood vessels going into a healthy adult human disc. So, all nutrients and waste products have to go in and out from the disc through diffusion. And by loading your disc, by having some physical activity, you can improve this exchange, which can also help to maintain tissue homeostasis. These cells in the tissue are very responsive to physical activity. And they have a bigger chance of maintaining the tissue if they get enough nutrients and if they get this mechanical stimuli that they need. So, an active lifestyle, like Dr. Stone said, not necessarily high intensity exercise, but just walking and being physically active is a good way of trying to keep your spine as healthy as possible.

Ashish Diwan, MBBS, Ph.D. So, Tom, this may be a good opportunity to do a reverse segue to what Laura and Lisbet have just said to the previous question that you had there, which was about risk factors, which might predispose to people in experiencing pain, and

whether there are health disparities. So, you know, when people talk about health disparities, they immediately go into the ethno-socioeconomic model. But I'll tell you what I see firsthand and what I experience and that relates directly to the activity issue that Laura and Lisbet mentioned. You have this group of people who leave school early, get into an apprentice mode, learn a trade, and become tradespeople and are in manual laboring jobs. And they start that when they are like 16 years old, right? As a surgeon, I start my career by the time I'm 36 or 40. And when I start my practice, I see a 40-year-old laborer whose back is busted. We build our countries on the back of these people. Right? By mid forties, they are just unable to work. So there is that extreme amount of physical activity in a constant twist turn mechanism. On one hand, it provides them with good musculature and strength. On the other hand, there is a structural deterioration that happens, which basically makes them non-functional. You know, you and I, as scientists and physicians, can be working in our late sixties and seventies. You will not find a tradesperson working on that. So, so that is one end of the spectrum.

The other group of people I see are the people who are in call centers and they're coders… and that's one of my children since he becomes a coder and what he's got, in his twenties, he is got back pain of a severe nature. So that is a disparity in terms of profession in the modern world that we see and that is getting teased off more and more. So that's one of the things that one needs to keep in mind and that kind of impact on their ability to look after the family. We have evidence in Australia that if that individual is a single income earner for the family and injures the back and actually goes on either social security if the workers compensation is over because that only lasts for a certain period of time. The median salary or medium income of the family drops below 60 percent of the average income for the nation, and that is a definition of poverty. So, back pain can cause that impact. It can disrupt families, and that by that time, the model that Laura mentioned is the bio-psycho-social-, economic, and consequential model. And that vicious circle becomes difficult to break. So the impact is humongous. The disability is humongous. At a given moment, 7.3 percent of the world's population has this pain disability. 7.3 percent is a massive thing and that happens irrespective of the OECD status or the economic status of the nation. It's a global phenomenon. So, these disparities need further teasing out in that sense to be able to identify the better population and how we get that activity to an optimum is something that we need to work on.

Lisbet Haglund, Ph.D. I think an important thing that you mentioned is that if you don't move enough, you get back pain. If you do too much exercise or hard work, you get back pain. So, exercise is really important, but there is a window. Not enough causes a problem, too much causes a problem. So, to find that window of a good amount of exercise is really critical. And I think that varies as well for younger individuals that are still growing. Very heavy exercise is not the same for a young individual as for an adult, as for an elderly person. So this type, what type of exercise, how much I think is also dependent on age, on sex, on a whole lot of things.

Ashish Diwan, MBBS, Ph.D. And communicating that in a clinical setting is a challenge. So, I try to simplify it when I'm talking to patients. Listen, you know, we've got a good Olympics team. We really don't want you to become an Olympian. So, we really don't want you to do that much of exercise. So, I'm like those at that spectrum. You already look fine, you know. You're trying to get your body into good fitness, you know, to attract somebody. Maybe you don't need that too. Then the third group is you just need to do exercise for health maintenance. And then the fourth group is you've had one back pain. All your muscles and all are decompensated. They probably have some fatty infiltration by now. So here we are going to use exercise to undo some of those bad effects. So it will be like a drug. And like any drug. If you take in too much dose, it is a poison, and every poison, if you take it in a

very low dose, somehow is a drug. So, people get that, and when they understand the impact of what it means, and Laura alluded to it that she does not want to use the word exercise and wants to maintain the word physical activity. The people to emphasize that dosing in that context becomes very important for an average person to understand what is it that I'm doing with this particular exercise or that particular exercise.

Nina Tang, Ph.D. I think that's a really good point. And thinking about exercise, I guess that leads on to our next question: what kind of treatments are patients offered clinically in terms of non-surgical and surgical? And when? Do they have to undergo surgery to treat their low back pain? At what point does that happen? And what considerations affects, say, a physician's decision to treat the condition non surgically first versus, like, going into surgery?

Ashish Diwan, MBBS, Ph.D. Thank you for that question, Nina. So, I think that is obviously directed to me, so I'll jump in and take that. So, when it comes to surgery, let's first understand what's the type of surgery we do. One is we take the pressure of nerves and we call it decompression. You know, words like posterior decompression, lumbar decompression, microdiscectomy, endoscopy, discectomy. These are the words that are used for that, and they are normally done for leg pain, and they can be done in an acute setting. The recommendation right now is that if you have had three weeks or six weeks of unremittent leg pain, go and get the discectomy done.

But it's a shared decision-making process. Somebody like me, if I have that lumbar disc herniation that Lisbet mentioned, the whole disc popping out and pressing on the nerve, I'll walk across to my colleague next door and say, remove it because I know I can be functional. But we don't do in the clinical setting that because it does get naturally better in about 70 percent people by the six-week mark. So we continue to manage it non operatively for some point. So that is a decompression relief of that nerve in that acute setting is a fairly personalized choice in a shared decision-making way that one needs to manage. There are patients who may say, do whatever you want to do, but do not touch my spine. So we continue managing them non operatively. We'll use physical therapy, we'll use drugs, we'll use injections, epidural steroids, we'll give them cortisone tapers orally. There's a whole range of stuff that we do. Some work, some do not work.

Then there's the other setting. Somebody has had chronic unremittent back pain, not been able to go to work, have already spent $5,000 adjusting the mattresses and reorganizing their home. And they're not making much headway with all this physical therapy, and they have unremitted back pain. They don't have leg pain. And they show some decrease in disc height, which is a good index of the degenerative disc disease. They show some subtle instability. Those are the ones that we start a decompression does not work. They need some sort of a stabilization. And that stabilization could either be in form of a total disc replacement, which has many contraindications, but more often than not, it is a spinal fusion in a minimally invasive manner nowadays. So that is when we get to a point where, again, under a shared decision making process, we arrive at a conclusion. We still lack clarity as to who will do good. We do not have any predictive analytic tools as to who will do very well with fusion and who will not. And that is an open question for us as surgeon-scientists to be researching and figuring out who's an ideal candidate.

But essentially, these are the two commonest type of operation we do. The third one that we do is called realignment of the spinal canal. Imagine somebody has had discal issues for numerous years and goes into decades, 10 years, 20 years or so, and they just collapsed on one side at L4-5 and then the opposite side at L3-4 and gradually have developed this scoliotic curve, which with the aging population is becoming an epidemic. We are seeing more and more of these patients. And they need what is called the third type of operation

that we do is the realignment of the spinal canal. We'll put in cages in the interbody space and put screws across in the pedicle and rods. We can do that all minimally invasive now, but still it is a major reconstruction and a major intervention into the human body.

Lisbet Haglund, Ph.D. I was wondering if now could be a good time as well to talk a little bit of the biological treatments that are starting to emerge, or that's been used a bit to, for the past five years perhaps. So, we have stem cells injections to the disc. We have platelet rich plasma injections to the discs. And these treatments seemed to have some positive effects in certain groups. But again, looking at the systematic reviews and the meta-analysis, the results are not great. And I think this is a big problem that I was alluding to before is that we don't know which patient will respond to this type of therapy. If we could stratify the patients better to understand which discs do still have enough cells to repair the tissue, which discs do still have enough nutrients coming into the tissue. So, if we inject stem cells, there's actually nutrients for the cells so they can survive and repair the tissue.

I think there's a lot of very fundamental things that we still need to understand to be able to target different treatments when it comes to the more biological treatments that would be done before you need to have a spinal fusion. So, I think that is a huge field where we need to really understand more. We need to have models, animal models and in vitro models, that can mimic these different scenarios. And then when we do clinical trials with the treatments that we select the right treatment. patients, because if we don't select the right patients, then the outcomes are not great. And it's not because it doesn't work, it's because we are treating the wrong patients. So, I think this is extremely important.

Laura Stone, Ph.D. There's a term “personalized medicine” and the kind of dream that I think we're all working towards is to be able to have enough understanding of what's causing the pain in each person so that we can match the best treatment for that person. And there's quite a bit of effort to identify biomarkers, which is basically anything that can be measured that might help us identify what's causing someone's pain or what treatment they will respond best to. And if the more we can match a treatment to the right individual, the better off we're going to be because it's such a complex condition. I hypothesize that some of the the statistics, many of the treatments are not very encouraging. They only work for a certain number of people. They don't work very much if you look at lots of people. And that's why potentially because we're just not matching the right treatment to the right person and what's causing their individual pain. So, this is really the pie in the sky dream is to be able to really match an effective treatment for the kind of pain that each person has.

Ashish Diwan, MBBS, Ph.D. I think our colleagues within the ORS and the largest sort of BACPAC and NIH Heal initiative, there's a fair bit of work. Laura, you are involved with it. Lisbet, you are also involved with it. Where we are looking at “omics.” Whether it is your particular gene, whether it is the metabolite in the blood, whether it is a marker in the MRI scan, some of which Lisbet alluded to, like modic changes and whether it is the microbiome, which sets all these things. Overlapping stories will probably help us get to that point of personalized medicine, where we will be able to identify those clusters of people. This person will do very well with drinking more milk, that person will do well with taking the milk out of their diet. This person will do very well with exercise. That person will do very well with this injection. This one is not going to do well with surgery. So hopefully, we will be able to tease that out.

But just taking a step back to Lisbet's commentary about biologics, I think that's a very, very important field where all our colleagues within the spine section in ORS are making major strides and major efforts. Because the current situation, and going back to my comment about surgery, is a person keeps on suffering with back pain. Not everybody gets better. You

have this about 10 people every week I see who have tried everything possible without surgery: injections, drugs, physical therapy, chiropractic, brace, everything they have done. For them to come to my rooms and be said that, well, your next step is to undergo this big operation where I'm going to put screws and bolts into you, that's a leap of faith: humongous. So, we have that gap in treatment, which we need to fill with something. And that's what we are all struggling with, which biologic will help. So, when we look at biologics, we are looking at three possible strategies, each one of them towards trying to solve the problem in a structural sense and in a sense of relieving pain.

So, one strategy is cell based. We've made some effort, whether it is platelets or stem cells, open to question. We don't think they may be a solution. We don't know whether inducible stem cells will have a solution, but we know that cells as such will have certain challenges, which are peculiar. The second group, or rather the third group, is scaffolds. And they are easy, everybody develops some sort of a collagen structure, or another polyglycolic acid, or a silicon based little microtubule, or a carbon nanotubule, and they want to stick in somewhere. And the disc is a good place to stick it in because it doesn't get washed out. One of the advantages of being avascular is that once you put it in there, it's not running off as it would from the knee joint.

But the third group where we, and even Lisbet's group and team, we see potential is a signaling molecule. Can we alter the signal there, which can then direct the cells to come and do their job, to create the scaffold? So, if we just modulate that signal, will that help? We have our own group is working on it. We have a recombinant protein that we know brings in the stem cells there and make some extracellular matrix from Canada. We have the N linked protein, which does similar things. There's another study, which is in phase one trial in the US. So, there's a lot of stuff happening around that signaling molecule scope. We have tried signaling molecules in the past. Off the shelf, one of the BMPs seven and twos, and they haven't worked, but there is hope. There is hope in getting that thing up and going. So I would say to the people out there that hang in there, something good will come up in the biological space.

Laura Stone, Ph.D. The intervertebral discs are also great candidates for viral vector therapy, so called gene therapy. If we can figure out in what way have these cells gone awry, we can actually use viruses injected directly into the disc to express different genes that can kind of help fix it. So, if there isn't a small molecule or a source of another kind of cells that we can put in the discs, there's a whole world of potential future opportunity using these viral gene delivery systems as well. And that's not really been explored in humans yet. It's still very developmental.

Nina Tang, Ph.D. So, I'm so glad we discussed all of these different aspects: the pain, cells, intervertebral discs, facet joints. This brings up one of the ultimate questions: what is the ultimate goal of treatment? Is it to repair the disease tissue or is it to treat pain? Because some patients can present clinically with severe IVD degeneration but no pain. So, is it still critical to treat that degeneration or is it more important to treat pain? And I want to get your opinions.

Laura Stone, Ph.D. I have a very strong opinion about this, which is that we really want to treat pain and improve quality of life. Individuals don't care if their discs are degenerating if it's not painful or causing some other kind of health problem. But one way that we know we can have some impact on the pain might be through repairing the tissue. But ultimately, the goal is to reduce pain and improve quality of life… however we can get there.

Lisbet Haglund, Ph.D. I think we all agree on that that it is the pain. But like Laura said, repairing the tissue might help reducing the pain because if the pain is coming from the tissue, if we repair the tissue, then we can treat the pain. But the end goal should always be to treat the pain and improve quality of life.

Ashish Diwan, MBBS, Ph.D. And I wouldn't say I'll take a contrarian view to that but I will share some experience. Nina, going back to your question, I think it is not a question of whether we should treat this and the Boolean factor, whether it is "OR", I think it is more "AND" rather than "OR."

I have this bunch of patients and I do a clinic once a month in a country town where the community is mostly farming community. And when they come in, they say "I can tolerate pain. Pain is not a problem. I lived with pain all my life. I'm unable to tolerate the disability, the disability means that I'm unable to do this, that, or the other." And the disability is mostly due to the structural piece. So, recreating that structure, you know, being anabolic and remembering very clearly that we are an orthopedic research society, and we are not an anti-inflammatory, rheumatological society where we have to just constantly suppress inflammation. As surgeons, we always think how fast can we repair a tissue? How can we regenerate a tissue? How can we replace a tissue so that that function is provided for? Because providing that function will improve disability. And improving the disability then improves quality of life. So, it has a significant contribution in the QOL.

Pain, they'll say "Okay, I'll manage it with another acetaminophen" or, I forget, what do you call it in the North America? We call it Panadol here. So, they can handle it. But getting that structural integrity is important because people are going to live longer. If we keep on letting their discs collapse, the spine keeps on getting deformed, and they keep on finding it very difficult getting in and out of their cars or living a life of where there is no support structure. Maybe they'll have a few robots to do the cleaning and all. It's going to be difficult. So we need to be focused on how we can keep the chassis of the body, that is the entire spinal column, in good shape for people to live 100 plus years and beyond. So, I think regenerating, repairing it, structural thing is very important too. And that is the expectation. That is the expectation from our patients and people who suffer, is that we keep that fixed to prevent that from degenerating.

Thomas Leahy, Ph.D. Well, thank you. We are closing towards the end of the hour, so I want to ask one final question. We've touched on this perhaps a bit already, but what are pressing questions or kind of the most pressing knowledge gaps that y'all would say need to be addressed in the next decade or so in order to improve clinical approaches or translate basic science research to the clinic for improving treatment of lower back pain?

And perhaps as part of your answer, if anyone has any closing remarks or things they haven't gotten a chance to say yet as a part of this interview series, it'd be excellent to hear any additional thoughts at this time as well.

Ashish Diwan, MBBS, Ph.D. So I'll start off with me. I'll just quickly say three things. In terms of innovation, where I think where we are targeted and where we are proceeding.

One is to decrease the stiffness of spinal fusions. I think there is a role for an elastomeric interbody device and the posterior dynamic stabilizer combined, which we call as soft interbody stabilizers. There are two companies, at least I know of, one in the U. S., one in Australia, which are making stride there, which should be kept an eye on. That is number one.

Number two is going back to Lisbet's original question of identifying which disc to treat. I think as discography and all are out of the door, finding a painful disc properly, that is important. And again, there is some post-processing MRI technology, which some people who are ex MIT grads are looking at bringing into clinical practice. That post-processing MRI scan would be cheaper and will be easily scalable. So, I'm excited about that.

And the third thing again, which Lisbet had mentioned earlier is that biological therapy, I'm very sort of bullish on the idea of having an intradiscal recombinant protein, which is based on some good solid signs to mobilize cells into the disc and take care of that group of populations so they don't have to go to spinal fusion. So, what are we trying to say is diagnose the discs better, number one. Number two, stop people from going towards spinal fusion. And number three, if they are going towards spinal fusion, decrease the stiffness so you don't get adjacent level problems. So, these are three major domains.

And just as parting comments to add: the role of diet is going to be big. I think we need to do a lot of work in that area. We need to look at the microbial configuration of a human body as to its impact. We need to look at prevention strategies, specifically smoking, and especially with this rising incidence of vaping all over the world, that needs a lot of public education. We need public health people to come up with robust public health solution. We know that physical activity does it, so they need to do something as harsh as shutting down social media and television for two hours every afternoon. You know, something revolutionary needs to happen there. So, those are my comments.

Laura Stone, Ph.D. I think the biggest knowledge gap is why do some people with a lot of wear and tear in their spines have pain and others do not. If we could understand that, that might provide a lot of insights into possible treatment interventions. And in a kind of closing remark… that was a great setup, thank you for mentioning diet and other quality of life lifestyle measures. I'd like to see a frameshift in how we think about chronic back pain and chronic pain in general towards a whole person model where we address the issues in the spine, but also address lifestyle. We try to help people reduce stress, improve diet, and be more physically active. Smoking is a huge risk factor for back pain, so that's another lifestyle intervention that could be addressed. So, this more holistic approach of treating the whole person, their habits as well as the underlying biology, is the way forward.

Lisbet Haglund, Ph.D. Perhaps I should go a little bit different way and go to a more molecular level. I think we need to understand what is causing the pain. It's one thing to treat the pain and treat the nervous system. But if we can't treat the factors that are causing the pain, it is just palliative. If we could really remove the factors that are causing the pain, and we have some ideas of what this could be. If we could do that, together with education about physical activity, about diet, about lifestyle, I think we could make a big headway. Together, with if we could better stratify the patients, so we understand who would respond to one treatment or the other and treat them early on before they need a big surgery.

Thomas Leahy, Ph.D: Awesome! With that, I think that brings us to a close unless anyone has anything else to add. I'd like to thank our speakers, Drs. Diwan, Stone, and Haglund, for being here and sharing their time with us today. It was awesome to hear your opinions on these super important concepts for the public and patients, as well as from a scientist point-of-view. I'd also like to thank Dr. Nina Tang for co-moderating this session with me. That was amazing. And finally, I'd like to thank the ORS Board of Directors and the Public Outreach Committee for supporting us putting together this interview series.

*****Transcription by Thomas Leahy (with automated assistance from Descript)*****