

June 27th, 2022 Patient Education Webinar- “When the Eyes Have It- Ophthalmology” Transcript

Amethyst: Welcome, everyone. I'm Amethyst Yale and I am the Community Engagement Manager here at the IPPF and I will be your host for today's webinar. Thank you for joining us. Today, we are joined by Dr. Robert Kelsch from Northwell Health for today's Patient Education Webinar. This call is now being recorded.

I would like to thank you for being on the call with us and to our Sponsors Sanofi Regeneron, Genentech, and argenx, and for making today's call possible. “Information is a key factor in treating and living with any condition. However, every patient's situation is unique. The IPPF reminds you that any information found on the internet or during presentations should be discussed with your own doctor or healthcare team to determine if it applies to your specific situation.” So, before we begin, we'd like to take a quick poll to see how many of you on the call with us today have consulted an oral pathologist or an oral medicine specialist in your pemphigus or pemphigoid care? And you'll see that pop up on your screen right now, if you don't mind taking that poll. I'd like to introduce you to our speaker for today.

Dr. Robert Kelsch graduated from UCONN School of Dental Medicine in 1992 and has been an active member of the AAOMP since 1994, and Fellow since 1997, completing his oral and maxillofacial pathology residency training at Northwell Health System, in 1997. Dr. Kelsch has been a Diplomate of ABOMP since 1999. Currently, he is an Associate Professor in the Departments of Dental Medicine and Pathology and Laboratory Medicine at Northwell Health, as well as Zucker School of Medicine at Hofstra/Northwell. He is actively involved in the oral and maxillofacial pathology residency training program, has a faculty practice in clinical oral pathology, serving as Director of Clinical Oral Pathology, in addition to participating in the oral pathology biopsy service. He has been invited to speak nationally at meetings including Yankee Dental, the Chicago Midwinter meeting and California Dental Association as well as presenting at AAOMP Annual Meetings. He is also a member of the Medical Advisory Council for the IPPF. Dr. Kelsch was recently elected as a Director in the American Board of Oral and Maxillofacial Pathology.

Thank you for taking the poll for us, and it looks like we're going to quickly share our results. Wow. Yes, definitely are interesting. So a good chunk of you have, and a good chunk of you have not.

For those of you who are on their computer for this webinar, you will see on your screen that you can access the audio either by using your telephone to call in or from your speakers and mic on your computer. As you see on my screen right now you have the option to select one or the other. Please be sure to select the method that you will be using.

Also, if you would like to ask a question please type your question into the text box under the questions section in your GoToWebinar sidebar. We received many pre submitted questions prior to the webinar as this is a very popular topic. We will try our best to answer as many questions as we can within the hour. On the webinar today we will be discussing oral care for Pemphigus and Pemphigoid. If you ask a question that does not pertain to the webinar subject I will have to ask you to email me after the webinar. For those of you on the call that aren't on the

web, you will not be able to ask a question. So if you would like to ask a question, please click on the link that was provided to you in your confirmation email.

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Now, it is my pleasure to introduce Dr. Kelsh to discuss oral care for Pemphigus and Pemphigoid and answer your questions for today. Thank you so much Dr. Kelsh for joining us.

Dr: Kelsh: Thank you so much. It's a pleasure to be with you this afternoon. I really do appreciate your asking me to discuss diseases which are of great interest, not only to myself, but certainly to you. People who have kindly joined this webinar this afternoon. My goal obviously is to discuss a lot of clinical related things with you. The clinical manifestations, which I'm sure for most of you, will not be a surprise, to kind of go through the approach that I would recommend that I use in evaluating and managing and diagnosing patients, and how we interface with both our medical colleagues and our dental colleagues. And then, obviously, provide some guidance for you, as to how you can best maintain your oral health, and go through your daily life, as asymptomatic and as healthy as possible. I will try to cover almost all topics from the diagnosis of Pemphigus and Pemphigoid. Treatment modalities, briefly, which I'm sure many of you have received what we can do as far as maintaining oral health. Both at home, with home care, and, certainly, what you might expect from care, provided by the dentist, or hygienist, or your dental office in your local community.

I would like to start with kind of a patient, and I'm sure this is going to be a circumstance that, unfortunately, is probably quite a common experience. And many of you may have come across this as well. In your, in your quest to ultimately get your diagnosis of Pemphigus or Pemphigoid for guiding the clinical history I would describe here is something that you're seeing here. This is a patient that I saw many years ago at this point. She presented with local ulcerations. Went to her dentist and was told she had canker sores, sometimes something got a little bit better, a little bit worse. And then, over time, she continued to develop more, and more and more lesions that were not going away on their own. At that point, she began her quest for finding out what is going on.

Unfortunately, her experience, as you can probably attest, was not a unique one in that it took her many, many months to finally get to a person such as myself, an oral pathologist to get the diagnosis of Pemphigus. Her history was that she had these oral lesions for approximately 18 months having seen multiple certainly dental professionals, including dentists, oral surgeons, and then kind of spiraling out into the medical community. And she saw rheumatology, primary care, EMTs, multiple EMTs, for that matter. And finally, kind of almost inadvertently and serendipitously happens, too, need some kind of care. That was completely unrelated and mentioned these oral lesions and somebody said, Well, you know, we have a new faculty at the dental school in Chicago who's an oral pathologist, and, you know, this might be something that he can help you with.

And sure enough, she saw me, came in and I knew right away that she had Pemphigus Vulgaris, you know, and how did I know that?

You know and I'm sure, you know, as I said, this is probably an experience that unfortunately, is all too common. And many of you may have experienced this long trajectory of trying to get to the bottom of why you have these persistent, really miserable oral sores. And obviously she had multifocal involvements, she had mucosal, she had soft palatable involvement. So basically, she had these lesions throughout her mouth. She had a positive nikolsky sign, which I use in trying to diagnose, because when we see patients that look like this, when I discuss this, I say most patients who present like this are going to have 1 of 3 conditions and we put them under the umbrella term of blistering conditions. And those three conditions are Pemphigus Vulgaris, Pemphigoid, which can look remarkably similar and lichen planus. But what I find when I'm doing a clinical examination is that patients who have Pemphigus or Pemphigoid, often have what we call a positive Nikolski sign. And since the blistering conditions, I can actually elicit a little either a blister or appealing or sloughing of the tissue, which I'm sure many of you have experienced when you're performing oral hygiene. You just kinda get sloughing and peeling of your tissue and that, I find, is a very helpful clinical sign when we're trying to determine a diagnosis. Here's an example of the positive nikolsky sign, which you're seeing on the lower left, where you can see we just take a little cotton, tobacco cater Q-tip, or cotton ball. And just kind of you can see how fragile that tissue is, leaving a denuded surface.

The picture you're seeing on the right hand side is a patient. And that whitish kind of sharply demarcated, irregular area is actually a collapse blister. So just like blisters you'd get in other parts of your skin like frictional blisters on your hands or feet, you know, these blisters can be fluid filled, or will be fluid filled. Which then when the fluid leaks out the roof of the blister, collapses down, leaving kind of a little piece of flabby tissue, which, because of the superficial nature of the blisters in the oral cavity, tend to be lost very quickly leaving the ulcers and erosions, which are the really painful lesions that you experience.

Although, historically, Pemphigus Vulgaris has been known for thousands of years. The ancient Greeks knew what Pemphigus Vulgaris was. Pemphigus Vulgaris basically means common blister. This condition has been known as a specific condition for many years, but classically described as a skin disease. And as you can see, this patient has significant dermatologic involvement. When she saw me, she, obviously, had tremendous oral involvement, as well. But, she had significant skin involvement. Now, what's interesting is, she was referred to me by her dermatologist. The dermatologist had evaluated this patient and made an assessment that her skin lesions were secondary to a longstanding fungal, dermatologic, fungal, infection, and not Pemphigus or any other particular disease and was treating the patient with topical and systemic antifungal with, obviously, no improvement.

When I saw this patient, you can obviously see, unfortunately, I don't have better intro oral pictures of this patient, because as you can anticipate, her entire oral cavity was just one blistering lesion. When I had a conversation with this patient and her son who was there at the appointment, for consultation. What was interesting was the comment that the oral lesions were noted before the skin lesions. And that's actually a quite common experience. So, although historically Pemphigus and Pemphigoid are described as skin diseases, and certainly you can have patients with skin manifestations, several of you on the call may have had, or currently have skin lesions, as well. In the vast majority, it's been reported up to 80% of patients, the oral

lesions pre-date any skin involvement. So, you know, here's where we have an opportunity, certainly in our dental world with a proper awareness of these conditions, to make a diagnosis of Pemphigus and Pemphigoid early before the involvement of the skin.

In my 25 now years of experience in oral pathology. What I would say is, if we identify the patients like yourself with oral lesions first, oftentimes with initiation of therapy, in a timely manner, we can often prevent, or at least minimize any skin involvement for each or either of those two particular conditions. In knowing that the oral lesions can present as the initial manifestation of these disease processes. It really puts the onus on our dental professionals to be aware of this particular condition. And I try to ring that bell all the time, when I speak to study clubs and other dental professions. Certainly, it is not necessarily just our rural pathology residents, who are learning what I do, But our general practice, and oral surgery residency, raise that awareness about these particular conditions, so that they have them in the back of their mind when they're seeing and evaluating patients.

So, when we saw this patient and we made the diagnosis, I'll get into the diagnosis part shortly and how we do that. Today, as palliser in the past and may mirror what? They may mirror what you are experiencing. When we get the patient on appropriate therapy, you can see that the lesions clear. So she did not have a skin infection or fungal infection, she in fact had Pemphigus Vulgaris with both oral and dermatologic involvement.

Again, I'm not going to get, I will talk about the, the diagnostic of and classically, we will get tissue samples, which we will look at either under the regular microscope, or we do very specific sophisticated testing called immuno fluorescence testing, and both Pemphigus and Pemphigoid have very specific patterns. Again, I'm not necessarily I don't think we have time to get into the specifics of the particular test, but each test is designed to identify the specific condition, so that we can tailor the appropriate treatment for the patient.

Pemphigoid when we talk about Pemphigoid I look at it as almost a sister condition, right. So both Pemphigus and Pemphigoid are considered autoimmune blistering diseases. So the concept is that, for some reason, your inflammatory cells, your inflammatory system is producing antibodies, which are usually used to combat infection. They're producing them to portions of yourself. In Pemphigus and Pemphigoid they are attacking very specific structures within the lining soft tissues where you will focus on the oral, but the lining soft tissues of the oral cavity causing them to be appreciated as foreign. And your body's attempt to kind of rid themselves rid itself of this foreign quote, unquote material on foreign tissue, almost as if this was like a rejection for a graft type of experience. And what happens is when the inflammatory response is quite brisk, you get the lesions that we see with Pemphigus and Pemphigoid and here's a patient that has very similar lesions to what we saw with Pemphigus and Pemphigoid. The difference, not only the difference between Pemphigus and Pemphigoid does not necessarily only on the clinical side, but also, obviously, they have different microscopic patterns that help us delineate which of the two conditions we're dealing with. The one thing that is more specific to the Pemphigoid patient, is the ocular involvement, because we know when we're dealing with Pemphigus and Pemphigoid there's a split within that lining surface epithelium. And that split occurs at very specific places. It's a much higher split in Pemphigus whereas it's a lower split closer to where the lining soft tissue meets the underlying tissues. So in Pemphigoid the term that we use for oral Pemphigoid is cicatricial. So when you get a split and a loss of the tissue the ulceration in Pemphigoid, what happens is that tissue heals with scarring. So what

can happen is any type of tissue that we call a mucosa. Your oral soft tissues, your nasal mucosa, your ocular mucosa, your cornea. Each of these can be affected, which is a distinction between Pemphigoid and Pemphigus. There is really no ocular involvement in Pemphigus, but it is something that we can see in Pemphigoid.

Now, that being said, what happens is with repeated breakdown of the soft tissues, you can wind up with scarring and scar bands that can affect the eyes and obviously, inhibit and change vision. So, when I see patients and we're making a diagnosis of Pemphigoid, I will often recommend an ophthalmology consult to make sure that there was no ocular or eye involvement of Pemphigoid. That being said, although we teach ocular involvement of Pemphigoid. I will tell you, in the 25 years of practice, I haven't had any patients in the recent past that I'm talking 10 to 15 years that have had any ocular involvement of Pemphigoid. So, while it is something that we need to be aware of, something that an ophthalmologist should evaluate for, it is not something that I'm seeing on a regular basis that is a problem for patients. Most of the issues are obviously oral that we manage. And the ocular has been very rare. I haven't had a patient who said to me, My ophthalmologist is telling me, I do have ocular Pemphigoid. So that's I guess, the saving grace with Pemphigoid.

Although we can see ocular involvement. It's not something that I'm seeing more recently. Again, Pemphigoid has this similar type of testing that we can do based on regular biopsy specimens with small samples of tissue, and these immunofluorescence tests which are the classic way that we can make a diagnosis of Pemphigus or Pemphigoid. Because clinically, they can look remarkably similar. I will tell you that, clinically, I find that with Pemphigus the oral soft tissues are involved, almost uniformly. Whereas, with Pemphigoid I find that there's a preponderance, a real significant gingival whole involvement. So a lot of patients with Pemphigoid, some of their manifestations may only be gingival involvement. They may have other smaller areas elsewhere. But it's not diffuse, it's much more of a gingival presentation. That where there's this beefy red gum tissue with ulcerations, kind of like what you're seeing in this patients are what we describe as a discriminative gingival appearance. Again, a lot of these patients, particularly with Pemphigoid since the gum tissues tend to be involved primarily. A lot of these patients' delay in diagnosis comes from the fact that the condition is not appreciated in the dental office. So, again, some of you may have gone through this experience, where you go to your dentist, you say Your gums are red, they're swollen, there's bleeding, it's hard to do oral hygiene. You go in and the dentist and hygienist do a very thorough cleaning. They do scaling, root planing, deep cleanings, all these kinds of things and you're not improving. You're doing all the oral hygiene measures that they're telling you to. You're going through your profees. You're going for all your cleanings. You're doing all the oral hygiene, both local and in the office, and you're still not improving. Oftentimes once that occurs, then the dentist says, Well, maybe you have some periodontal disease and they may shut you off to the periodontist, at which point, the periodontist kind of recapitulates the same things. They're doing bigger procedures, maybe they're doing some surgical procedures, removing excess tissue thinking that this is a periodontal true conventional periodontal gum disease patient, and again, you're not going to get any better. And that's at the point where the periodontist will say, Hmm, maybe this is not related, just oral hygiene and bone loss and routine gum disease. Maybe this is something different, and that's when these patients like yourself, will make their way to my type of practice.

In which case, I will assess the patient, see this, do the positive nikolsky sign, and then at least have a clinical suspicion about what we're talking about as far as a diagnosis.

Again, some of you may have had gum tissues that looked remarkably similar to this. Raw, red, bleeding, tender, impossible to perform oral hygiene at home as best as you may try your flossing and it's bleeding. The more you floss, the more you're bleeding. You're doing the best you can with oral hygiene locally with really little to no improvement despite your best attempts. Again you can have gingiva gum tissues that look like this. And this is the kind of clinical appearance that I often see with a Pemphigoid patient. Kinda this red, gingival tissue. And, again, at first glance, a general dentist may say well if you look, and it's from my perspective, it isn't just the regular gum tissue that's affected. You can see that this is going beyond where just routine, periodontal gum disease would be. So that would be a key feature that I would look for in that regard to see that we're dealing with something beyond just routine gum disease. Again, but this patient can also have lesions in other parts of the oral cavity as well. As many of you may have experienced, these oral ulcers and lesions are exquisitely painful and tender and really prevent you from functioning normally with difficulty swallowing difficulty functioning. The tissues are very fragile and the tissues tear easily. Those are the things that we look for to make the diagnosis. So that's kind of like the intro and I'm sure many of you have had experiences like I described.

As an oral pathologist, what do we address? How do I teach, what do I suggest? What should you expect when you may have Pemphigus or Pemphigoid and you're presenting to the Dental Office? I'm going to address some of the questions that haven't previously diagnosed this. My hope is certainly to answer that is, I would hope. Dental students, dental residents, are taught about Pemphigus and Pemphigoid in their dental training. The answer I'd say is yes. Will they be able to specifically make the diagnosis? No, But my comment to my students in my residence is that they should be able to understand the difference between what's normal gum disease, and what's something different. And I'm not saying they have to come down and say, you absolutely have PemphigusVulgaris or Pemphigoid or Lichen Planus and jump into the treatment. There are people, like myself, who are available, who, this is what we do, and it's my goal that the dentist and hygienist in the office and the dental, the dental staff, are aware that not everything is just gum disease. So while they may not be able to diagnose it specifically, because we need to do the diagnostic testing, they should be suspicious when the local measures that they are performing are not working. So again, it's the awareness. Is the dentist aware of the condition, is the hygienist aware of the condition. The answer is, they should be. Another question was, how do we make the diagnosis? Traditionally, the diagnosis was made on a biopsy or a tissue sample that was removed from the gum or any affected tissue in the oral cavity. A small local anesthesia is administered when a tissue sample is removed and placed into a fixative and then sent to an oral pathologist for diagnosis.

Amethyst: Dr. Kelsh, do you need us to advance your slides for you?

Dr. Kelsh: Yeah, would you mind, I don't know what happened, something just kicked in, and now it's strange.

Amethyst: We'll take it back over.

Dr. Kelsh: So you can go to the next slide, which is the diagnosis slide. Sorry about that a little computer glitch. I guess that's the one drawback of not being able to do these all in person. Anyway, so how do we make that diagnosis? We were talking about tissue samples the conventional way. If the tissue sample could really be removed by somebody like myself who is in a hospital based setting. What would help is we can freeze the tissue, and then we can do those very specific tests that we said, immunofluorescence testing. But most of the time, the specimens will come from an outside, say, an oral surgeon. The dentist refers the patient to the oral surgeon, the oral surgeon does the biopsy and then we get the specimen and then we can process the tissue routinely and we can see the specific microscopic pattern to make the diagnosis. So that was traditionally, that certainly is what we say a gold standard, as far as making the diagnosis. And I'm sure that's how many of you may have had the diagnosis made based on tissue sampling. However, fortunately in the more recent past, we've had the opportunity to have serology or blood testing for very specific antibodies that are present, either in Pemphigus and Pemphigoid. For Pemphigus they're the desmoglein antibodies one and the desmoglein three. And for Pemphigoid its Bullous Pemphigoid 180 and Bullous Pemphigoid 230. So, what will I do? It is an initial assessment as I may have a clinical diagnosis of Pemphigus or Pemphigoid, and then I will run the serology because not necessarily every patient does prepare at a consultation visit to have a biopsy. Either they are nervous about having a biopsy, they want to have somebody there for support, or they may need antibiotic prophylaxis because they may have had a heart valve replacement, or they may have a joint replacement. So we can't do the biopsy at the time of consultation because they'd need antibiotic prophylaxis prior to any surgical procedure. So, what I've been taking to do now is recommending these blood tests and seeing what happens. If then one or the other comes back positive, then we have a presumptive diagnosis of Pemphigus or Pemphigoid. And then we can begin a treatment at that point. We'll talk about treatment shortly. Yeah, we can always do the biopsy at a different time. So I've been using, as a primary resource, getting the blood tests done for patients. But, as far as the biopsy by when and by whom, obviously, it would be early in a biopsy at its earliest convenience. If necessary and by whom? I train dental residence, dental students. And I say that if you can extract a tooth, if you can take a tooth out, you can probably do a biopsy for Pemphigus or Pemphigoid. It's really the clinician's comfort level. Oftentimes, a dentist doesn't like to quote unquote biopsies. So they often refer them out to an oral surgeon, or to an oral pathologist like myself.

Once the diagnosis has been made, in whichever fashion, we actually have made it, then, now, who manages these, who manages Pemphigus and Pemphigoid patients? So, certainly as a pathologist, we are trained specifically to manage patients in which becomes an interesting conversation in and of itself because orifice pathology is a very very small specialty of dentistry. And not every geographic locale has ready and easy access, much to our disappointment as an organization. We're a very academic specialty. So, a lot of us are based in either dental schools, or hospitals, or some type of academic institutions are not necessarily as readily available. For example, if you're in North Dakota, I don't believe that there is an oral pathologist within the State of North Dakota. So, who's going to manage that? I guess it depends a lot on our oral surgery colleagues, shoulder that burden in more rural, or suburban areas where there isn't necessarily access to an academic medical center. There is an academic medical center. There isn't necessarily any oral pathologist available. Obviously, the goal certainly as an oral

pathologist would be to somebody like myself or to be managing the patient. Because, again, most dentists I do not think would feel comfortable managing the oral manifestations of Pemphigus and Pemphigoid and treating those conditions as needed.

Next slide, please. Ok, that being said, what do we do? What do we do in the Dental office? What do we have available in the dental office? The questions that have been posed are- do I get cleaning? When do I get them? Can I get a cleaning when there is active disease, do I need longer appointments, and what type of cleaning do I get? How do we prevent bleeding? What do we do about my gingival health? Because the gingival and the gum tissue, whether you're talking about Pemphigus or Pemphigoid are frequently, and again, sometimes exclusively affected. That really becomes a very pertinent question. These issues become very, very pertinent. When I'm seeing patients and I'm making the diagnosis and we're in the early stages of management of Pemphigus and Pemphigoid my recommendation for a patient is to avoid any dental cleanings and prophylaxis until we clear the disease as best we can. In the early stages I have found two patients who have gone through dental treatment while having active disease and active lesions. They find and I have found that getting dental treatment during the active phase of disease exacerbates the disease. So, certainly in the early management stages, when you have an active disease, any treatment I suggest is put on hold until we clear the lesions and the lesions are cleared and you're comfortable, what will I say to patients to do? Well, once you're clear, certainly you don't expect to have the same level of pain and bleeding and gingival irritation and break down then when you had active disease. So, you can go back to a more regular dental type of cleaning prophylaxis appointment schedule. The longer appointments I guess would depend on your own individual level of periodontal disease at the time. Some patients had pre existing periodontal disease with bigger pocketing depths, and a lot of calculus and accumulation on the teeth. So, those longer appointments might have been needed, not necessarily because of the Pemphigus and Pemphigoid but because of your pre existing periodontal disease. Obviously, when you're well controlled with your Pemphigus or Pemphigoid and you're performing and you're able to perform normal oral hygiene, you shouldn't get the same level of bleeding or breakdown and you should mean you should be able to maintain your gingival health once the lesions are clear and you're comfortable. There shouldn't be much in the way of pain. You know, just as a recap, as I would say, when you have an active disease, hold off on any regular dental care. I mean, certainly if it's an emergency, you need a tooth out, You have a broken tooth: that's fractured, and you're in pain from my dental infection, or something. Obviously, you can choose to seek care, I would say, to take care of that. But I'm talking more in the regular, like routine dental, recall visit type of dental care, I'd put off on the hold at that point. But I do tell patients it is when you're clear for regardless of what the treatment is that we've gotten to the point where you are clear of lesions. What I do tell patients is particularly when we're using topical steroids, or maybe low dose pill steroids, which we'll talk about management in a moment. I would say, if you're using topical steroids, you may want to use them a little bit more frequently a few days before your appointment, the day of your appointment and for a few days after your appointment to prevent a flare. It's hard to predict. Some patients go and they get back on their dental care regimen and everything's great, they're cleared of lesions. They go for their dental cleanings and everything is fine and some patients will note that. Even though they're clear of lesions. Once they've gotten kind of a really thorough cleaning from the dental office, they get a little bump up when they start to get some lesions.

And I find that enhancing use of some of the medications that we'll talk about in a moment is quite helpful and tamping down or minimizing any potential flare of lesions.

Next slide, please. Home care, obviously the home care is going to be very variable, depending on the disease activity. Certainly, the goal is to be brushing your teeth 2 to 3 times per day, using dental floss as best you can. But when you have a big flare or you're in the early stages, where you have a lot of active lesions, that can be quite problematic because it's going to be a misery. You're going to be hurt and it's uncomfortable, you'll be in pain. So basically, it's the best you can. What I will suggest, for patients who have active disease, is no alcohol containing mouthwashes, because they're just gonna burn and hurt. You're gonna wanna avoid anything with alcohol. If you need a mouthwash, alcohol free mouthwash. If you just need to kinda rinse your mouth, warm salt water rinses just to kind of provide a little bit of a soothing back. Do the best oral hygiene you can. Soft toothbrush. What I do recommend is children's toothpaste. Usually it has the fluoride in it, which is helpful just for cavity prevention. But it doesn't have a lot of the other chemicals like that we see in a lot of the toothpastes that are marketed today. I mean there's a lot of whitenings and peroxide, and baking soda. There's all kinds of tartar controls and all other chemicals that are in toothpaste, which can be quite caustic. And the last thing that you want, when your gingiva is red and inflamed and ulcerated from Pemphigus or Pemphigoid is to now be applying these irritating chemicals on top of an already irritated oral soft tissue. In this type of circumstance, a home care, less is more. You want to try to perform as best you can. Sometimes I'll even recommend if somebody's just so involved with oral lesions, I'll recommend what we call a little too that. You can buy these in the drugstore. It's basically a little sponge on a little stick. And you can just kind of get in there. And just kinda gently remove any surface debris from your teeth and gums. What I do tell patients is you do not, and again, some patients their oral hygiene their standard oral hygiene regimen involves brushing both their teeth and their gum tissue. In your circumstance with Pemphigus or Pemphigoid I would regard against that because although we don't anticipate to have significant bone loss and periodontal loss with Pemphigus or Pemphigoid. If you are aggressively brushing your gingival tissues. Yes, you can cause some gingival recession. And like I said, sometimes when the gingival is swollen at the time you have active disease once the gingival and the gum tissue is returned to health. You'll say, Oh my gingival is receding. I'm getting receding gums and it's just because of the swelling that was there during the active phase of the disease, a kind of major gum tissue with vigor. And as you got back to health and your gingival tissues came back to normal, they looked smaller and look like though your getting a gingival recession. So you have to be mindful of that. Gentle, gentle oral care. Children's toothpaste, no alcohol containing mouthwashes, as best you can.

Any foods to avoid? Any triggers? There are no known specific triggers for Pemphigus and Pemphigoid. So there's really no foods to avoid, aside from common sense type of things. If you have an active oral ulcer or lesions, the last thing you may want to do is start crunching on tortilla chips. Anything that's really crunchy that can tear the soft tissues, So when you have active disease, more of a softer diet. But certainly, you want to maintain your hydration. So water intake is very important. And then caloric intake. You want to make sure you're getting caloric intake as well. Whether it's ensure, or some kind of protein type shake, some nutritional shake, something along those lines. Particularly when you're in the early stages and getting anything down is a misery because you just have a mouthful of sores. You do want to try and

maintain your caloric intake. The last thing you want to do is start losing a lot of weight because you're not eating because your mouth is so sore.

Next slide. How do we treat Pemphigus or Pemphigoid? Obviously it's an incredibly important topic that can go on for a long time. But I find that treatment for Pemphigus or Pemphigoid is multimodal. So there's multiple ways to kind of come at treatment. So certainly, you can use in the first line therapy today, or particularly for Pemphigus even today would be considered systemic steroids, so a pill type of steroids, like prednisone. Depending on your severity of disease, and again, the focus is that you're having oral lesions only with this know systemic. There's no skin involvement we're going to talk about. You came in, we have oral lesions and oral lesions only, or maybe very limited skin involvement, we'll put you the suggested treatment. Depending on the severity and involvement of the wall soft tissues, you might be between 20 and 60 milligrams of prednisone a day. The dosing It seems like such a very wide range in the dosing regimen because again, it depends on the severity of your disease. So it's a very individualized approach. So as well as other underlying medical issues, that might make you have to use a lower dose at the onset, particularly if you're a diabetic. A diabetic, one of the unfortunate side effects of prednisone and steroids therapy is an increase in blood sugar. And the last thing that may want to do in a patient who has uncontrolled diabetes and sugars a 400 is now place you on steroids which is going to put your sugars to 800. So we have to be very mindful of your basic underlying medical history so that we don't exacerbate or worsen any other underlying diseases. Steroids are very good in particular for Pemphigus and if you are an otherwise healthy individual with no other comorbidities, or underlying medical issues that would prevent us from using prednisone that is often a great first line therapy. And that therapy will be your main therapy until you clear lesions. Which depending on the individual, depending on how long you've had lesions on before you've had the diagnosis. And I find that patients like that patient I showed you in the very beginning, who had 18 months of no diagnosis, it took us a long time to get her where her lesions were clear. So, if you have a patient who has that type of history, or you are that patient, you can anticipate that high dose of steroids may be necessary for a longer period of time than somebody who maybe only have lesions and with the delay from the initial lesion to the diagnosis was a month. Patients with a shorter duration of this disease tend to respond much faster because the disease is not as entrenched in that. So again, it's variable on the, on the individual, and your other underlying medical issues. And again, we try to minimize the steroid dose to avoid any other steroids side effects that go along with long term use of steroids. We'll avoid that. There are patients today, if you cannot use a pill form of steroids or as an additional medication. There are things called, there's something called Rituxan or Rituximab which was initially used for rheumatoid arthritis and is FDA approved drug for the past several years for treatment of Pemphigus and Pemphigoid. So, you may be on this medication. You may want to talk to your physician, rheumatologists. That's an infusion medication that's used and I've had several patients that have gone on that either because they weren't responding to steroids any longer, or we only got a certain response. Say we got 80% response, but never 100% clearance we prefer those over patients who no longer responded to steroids. One of the things that I do use, regardless, of whether you're getting Rituxan or Prednisone, is topical steroids. So topical steroids comment on a variety of formulations and potency. There are low potency topical steroids like the hydrocortisone that you can buy over the counter for a bug bite or an itchy skin condition. And then there are high potency topical

steroids, like clobetasol. So that's a very high potency of topical steroids. So I would tend to use either clobetasol or something called fluocinonide and that's a mid to high potency, topical steroid for oral lesions. They work for patients with limited disease, or maybe a small breakthrough. You've been great, everything looks terrific, you got a cleaning. And you get a little bit of breakthrough, but you don't want to have to go back on prednisone. And you certainly are not getting another Rituxan infusion for another six months for your maintenance. The topical steroids fit a nice little window right in in that particular aspect of treatment. I will have patients use this throughout their care. You know the comments that I use regarding topical steroids is how can you apply them? Patients will use Q-tips, patients will use their fingers. Patients can get dexamethasone. You can also use dexamethasone, which comes as an elixir and as a rinse. Whatever you use, depending on the formulation, one thing how I recommend the use of steroids, topical steroids, regardless of which one, is make sure that we're using a gel based steroids, right? Steroids come in creams, they come in ointments, they come in gel based formulations. The creams and ointments I find do not work very well on the oral application to the oral soft tissues gel based steroids work much better because they are water soluble so they work a lot easier and they move around a lot easier. So whatever topical steroid that suggests to be used, it would be best if it's in a gel based. I'm sure many of you may have gotten the triamcinolone and or a base or the catalog and oral base, which is the dental paste, steroid dental paste. I rarely, if ever, use that, the dental paste, I find is not very helpful or usable. So you can put it in that way. Some people will have their dentist make custom medication trays, and that's certainly helpful. The problem is they're usually very form fitting because they are custom made to your gingival contours to your teeth. So in the early parts, you may find it very difficult because they may, because they're so form fitting. They may irritate and cut your gum tissues when you go to put them in. So, it can be a little bit of a double edged sword with the medication tray. I don't routinely have patients make medication trays. I have them apply it directly to the affected areas, with their finger, or a q-tip, and that seems to work very, very well. As far as treatments. So those are the treatments I would use for Pemphigus and Pemphigoid. Since most visits, gingival involvement. You can use systemic steroids, you can put patients on prednisone. However, I find that a little bit sometimes a more conservative approach with use of the topical steroids. In addition to doxycycline 20 milligram tablets work very well in managing most cases of Pemphigoid and we don't need to go to the pill steroids, prednisone route for most patients. So, there's a subtle difference in the management between Pemphigus and Pemphigoid in my clinical practice.

Next slide. OK, so that ends the presentation that I had, I've been more than willing to take any questions that we have. Hopefully, I covered a lot of the questions that you may have had in the discussion, but I'd be happy to address any questions that we may have.

Amethyst: Great. Thank you, Dr. Kelsh. That was a great presentation, very thorough, so I definitely learned a lot. We did get plenty of questions coming on the webinars, so I'm gonna just quickly start here. One of the big questions that we get here at the Foundation and also submitted, she asks, Will oral lesions become cancerous eventually?

Dr. Kelsh: The answer to that is no. There is no pre cancerous potential for Pemphigus and Pemphigoid.

Amethyst: Great. Thank you so much. Also, I know that you said during pretty active, active flares or active disease that you don't recommend that patients get a lot of cleanings and whatnot. But afterwards, how frequently do you suggest that they visit the dentist and how long should those appointments be taking?

Dr. Kelsh: I think you can go, probably, if you're clear, and everything has been good, you can probably go back onto your regular, or whatever your regular recall visit was. Again, that's going to be dependent on what you are pre diagnosis. Level of periodontal gum disease was, I mean, if you are a big periodontal per patient who had periodontal surgeries and you have 7 or 8 mm pockets and they're really trying to manage your periodontal disease. You're probably going to be either in the periodontist office or you're going to be back with the general dentist, maybe on a three month recall type of appointment. But if you're a 45 year old person who has 3 to 4 mm pocketing. Kind of like if you're just having that you have a little bit of periodontal disease, a little bit of gum disease, maybe a little bit of gingival recession, but no real severe periodontal disease. Probably at your routine six month cleaning appointment where you recall is fine because obviously one thing I didn't mention is like, we have you clearly we've cleared you, with a major diagnosis, given you the treatment. We've cleared your disease. What's your follow up with the oral pathologists? So, my patients when I'm making the initial diagnosis, I'm seeing patients usually on a monthly basis just to kind of gauge a sense of our improvement over time to make sure the treatment that we're providing is working. It doesn't make sense to continue on the same road if you know I have 160 milligrams of prednisone and it's three months later and you're not getting any improvement. So, to push you off that long, I want to get a sense of guideline over time. But, let's say, I know we've gotten to the point where it's six months out. You've been clear for three months of lesions. We're on a low dose of medication, regardless of what our treatment approaches at that point. Now, I'm going to end up following you initially probably every 3 months initially because I want to get a sense of a track record of how long we go before we have any flare-up lesions. So I usually initially for the first year once we've cleared, see the patient every three months, and if we don't have any lesions in that year you're well maintained, maybe only a couple of days of blip flares here and there. Then, I'll put you on a six month recall. There are other people looking, so I'll be seeing you, your dentist will be seeing you. So if you come to see me on a three month visit, and I say you're cleared of lesions, but you have regular gum disease issues. I may say, you might want to call up your dentist or your periodontist and get that cleaning. And oh it's not scheduled for October, well, why don't you give them a call and see if you can move that up for appointments, so there's definitely oversight from that perspective. So once you're cleared of lesions, that's not like your oral pathologist is saying, ok great, see you later. I mean, we are following you regularly over time, and making assessments ongoing. And we can fine tune how often you meet your profees. But what I'd say is if you're clear and everything's looking good, you are on minimal medications, and you feel great. Then going back on whatever the regular recall schedule you had before you had the disease is probably appropriate.

Amethyst: Great, thank you, that makes a lot of sense. Speaking of the team approach, Nancy asks, She does see her dentist for PV. And her dentists recommend that she sees a rheumatologist. Do you think that would be helpful for her as well?

Dr. Kelsh: Not knowing where she is geographically. It's hard to answer that question because it is an immune mediated disease. So, in her geographic locale, the rheumatology people might have experience. I know I've had all manner of medical specialists refer patients for Pemphigus. Interestingly enough though, the smallest, the one I would think would probably be the most interested in managing would have been the dermatologist. Interestingly enough, considering there are potential dermatologic manifestations, but most dermatologists, they don't really see this, interestingly enough. And at least here in the New York Metro area, most of the patients that I'm getting referred to, are not necessarily from dermatology. They're coming from oral surgeons, the oral care people are sending patients. So, I say that if you're a rheumatologist of the rheumatologists has some level of knowledge and interests, I don't see that's an inappropriate way to manage. Because a lot of times, the rheumatologists are involved with the people who can infuse of you. If you're a patient that needs Rituxan infusions. Initially when Rituxan's available and we were using we were getting our Pemphigus patients. And before it was FDA approved for Pemphigus and Pemphigoid we worked with medical oncology. So here I am an oral pathologist with a Pemphigus patients and I'm getting them over to medical oncology to get a Rituxan infusion: why, because they're the ones doing the infusions for all the chemotherapeutics. Rheumatologists treating a patient with rheumatoid arthritis with Rituxan probably has a pretty good understanding of at least how the medication works and can work with the patient. They may not necessarily have the best understanding of Pemphigus or Pemphigoid, but they certainly understand inflammatory disease and autoimmune disease in general and may be involved with an infusion center who will be the one infusing the Rituxan if need be. I don't think that's inappropriate management.

Amethyst: Great, thank you. Robert asked, is there any way to heal or rebuild or recover some of that gingival loss from Pemphigus or Pemphigoid?

Dr. Kelsh: Good question, and I do get this question on a regular basis, said, Oh, well, if I have a gingival recession, what happens after? And what I say to patients is because a lot of patients are coming to me from a Periodontist office because they are thinking that this is periodontal disease, and they need to do gingival surgeries and periodontal surgeries to correct the periodontal disease. Some patients have had periodontal surgeries on the books in the periodontal office or the dental office. Pre-dating our management of them with Pemphigus or Pemphigoid and I tell them, hold off on that until we clear you. Once the disease is cleared, we can reassess what the gingival level is. In all honesty, if you have cleared all your lesions and you're not having any disease manifestations. And disease activity is 0 to 2 minimal. You should be able to undergo any procedure that you would have had. That would have predated your diagnosis of Pemphigus or Pemphigoid. So, gingival grafting procedures which would reconstitute your gum tissue. I wouldn't say it's something that you would jump to, because we don't necessarily know specifically what's going to happen to you. But certainly, if you have a lot of gingival recession, but your disease free, you should probably have maybe, not exactly the same success level as somebody that didn't have Pemphigus or Pemphigoid but I would say that you are certainly a candidate, I wouldn't necessarily say its contraindications to having any periodontal surgical procedures. I would just add that obviously the periodontist who's going to be doing them needs to be mindful the you have Pemphigus or Pemphigoid. We have to

minimize any potential flare ups because you don't want to pay money to have a periodontal graft place to replace your gingival issues. That may or may not have been lost due to Pemphigus or Pemphigoid or just regular periodontal disease. You'll want to make sure that if you're having these procedures, that there's going to be some level of success. So certainly no procedures while you have active disease. That would be an out. But when you're clear, I would think that you'd be a candidate with the understanding that there's a possibility that it might not necessarily be the most successful result. If you're willing to take that chance. I think you have a good chance of it doing well. But there's this chance that it may not necessarily be the most effective procedure. But unfortunately, you're not going to know that until after the procedure.

Amethyst: Great, Thank you. Speaking of surgical procedures, we get this question a lot. What about recommendations for implants for people with Pemphigoid?

Dr. Kelsh: Again, when you're active disease, I say avoid any and all surgical procedures, because not that the implant won't integrate, I mean because Pemphigus or Pemphigoid or soft tissue diseases, and surface soft tissue diseases. They're not involving the bones, So theoretically having an implant placed would be successful because the implant itself will integrate into the bone, which is perfectly fine and normal. The soft tissue healing would be compromised, potentially. And if you have an active disease the last thing you're going to want is more surgical manipulation of an area that's already irritated and swollen, and tender and bleeding. But certainly again, that same point, once disease has cleared and your gum tissues are back to the baseline normal then any procedure would be appropriate. I mean, there's no contraindication to getting implants or anything like that. So certainly, you can proceed with any dental treatment or implant procedure. Again, with the same caveat that whoever's doing that surgery needs to know your underlying diagnosis. That your soft tissues could be at risk or slower healing because of your underlying disease. And if you get a flare afterwards, that may need to be managed and that could delay at least soft tissue healing in that area. but for implants the bone is fine, so they can place the implant, no problem. It's really your own comfort level. Technically, you could go and get an implant in the middle of a big flare of Pemphigus. I guess my common sense would be, why would you? Wait till things are cleared. And then just go about your business.

Amethyst: Great, thank you. We get a lot of questions regarding insurance issues. Pemphigus and Pemphigoid are medical issues. Is there a better way to seek coverage for claims under medical insurance rather than like dental insurance?

Dr. Kelsh: Absolutely. I will tell you that even if your dentist, or oral surgeon, or periodontist is very interested and knows a lot about Pemphigus and Pemphigoid, most of the dental offices are billing dental insurance. The way dental insurance is structured is very different, at least currently from medical insurance. So, when you bill dental insurance, it's basically billing a procedure code. They're billing for a filling, a cleaning. They're billing for an actual procedure that has been done. So there's really no way to bill dental insurance for Pemphigus or Pemphigoid because you're managing a diagnosis, not a treatment, you could certainly bill the dental insurance for the biopsy procedure that was done. If it's your dentist who wants to

manage your Pemphigus, basically their follow up visits with you, are going to be just dental, follow up visit codes. Which is what most dentists will bill. But the reimbursement rate is very low for those. So, that's why medical insurance is certainly the more appropriate way, because how medical insurance works is there are two codes to bill medical insurance. There are two codes that need to be placed on the insurance claim form or electronic submission of claims. And one is the procedure code. Is it a biopsy procedure? Is it a consultation visit? Is it a follow-up visit? So, those are the procedures. What is the doctor doing? But that has to be tied to a diagnosis code. So there's a book called ICD 10, which is the diagnosis codes, and that lists thousands and thousands and thousands of diagnoses for all kinds of medical related diseases. And so if you're seeing your physician or a medical colleague, they should be able to bill medical procedure codes and the medical diagnosis codes to your medical insurance for reimbursement. So, there shouldn't be any issue. The code that they would have to use for consultation, is usually a 99203 For a follow up is a 99213, and I don't know the specific the biopsy code is specific to a location, so I don't know those off the top of my head, but certainly, the diagnosis codes are L 10 and L 12.1. So, those are the diagnosis codes. Somebody has to have the procedure code and a diagnosis code has to be on the medical submission claim form. I will tell you that dentists, and surgeons, and people in the dental community, for the most part, do not bill medical insurance: They are not credentialed to bill Medical Insurance. They are not on the Medical plan. So, that's why if you're trying to have your dentist or oral surgeon or periodontist, bill the medical insurer for your diagnosis of Pemphigus or Pemphigoid that's why those claims not getting paid. Because they're probably trying to submit dental claims to the medical insurer and the medical insurer will not recognize dental claims for reimbursement. So, it has to be on a medical claim form and they may not even write, they may even use it. The claim with medical codes from with with medical procedure code and a medical diagnosis code, but you're not a credentialed provider for that insurer. It will be considered, probably an out of network benefit as because you're not a provider under that panel, that insurer that XYZ insurance, medical insurance, you're not a provider, under that plan, for that medical insurance for that patient. So, you'd be considered an out of network provider, and again, that's going to depend on whether the patient has out of network benefits. There are some plans here in the New York metro area, and again, that's going to be variable, depending on your geographic location. But, you know, we have some medical plans here that have zero out of network benefits. So it becomes a fee for service. So, unless you are seeing somebody that is very limited in our own provider panel for them to submit a claim, that patient will get zero out of network benefits. And basically, any procedures done by whatever clinician, that's not a participating provider, would be a fee for service.

Amethyst: Great. Thank you. That makes a lot of sense. I know we've quickly gone over an hour, so if you don't mind, ask two more questions. Somebody asked, Would you recommend that patients on immunosuppressive medications have a round of antibiotics before they undergo a dental cleaning or procedure?

Dr. Kelsh: Not necessary. Unless you have a pre-existing medical condition like a heart valve replacement or a joint replacement that wouldn't be required for those purposes. But for biopsy, surgical procedures, and routine dental care, it's unnecessary.

Amethyst: Great. Thank you. Bill and Rosemary asked, what are your thoughts on the electric toothbrush as long as it's soft and kinda moves in the circular pattern? And what about things like a water Pik, or a water flosser?

Dr. Kelsh: I think that they have their place. Let me attack like the water pick type of things, where it's water coming out as an irrigation. I find those can be helpful for patients on the lowest setting. Again, because if you have it come out too vigorously, you run the risk of traumatizing the common tissue and creating blisters. So, if you put it on the lowest setting and just be really careful around the gum line, I think you should be fine with the irrigation. It'll remove debris. A lot of times, you can put in other things, you can put in things in the liquid. You can put some salt water in there so it can kind of be a salt water irrigation. I wouldn't put much more. I mean, I know there's a lot of different things that are available that you can kind of put in to mix in with the water that can kind of irrigate. I think you probably want to keep it simple with that. As far as rotary toothbrushes or electric powered toothbrushes, I tell patients to probably avoid those. Certainly while they have active disease, for the simple reason being, I have noticed this and it's not just Pemphigus and Pemphigoid patients. I find that most people, when they first learned to brush their teeth they used a manual toothbrush. So, when we were kids and young adults, we started to brush our teeth. And some people push gently, some people push hard to remove the debris. But you can kind of fine tune that a little bit. What I find is patients who use rotary toothbrushes don't let the rotary do the job. Not only do they have the rotating bristles but they're also pushing like they did with a manual toothbrush. So you're kind of giving a double whammy in that regard. Right? Theoretically, when you're using rotary, toothbrushes, some kind of propelled toothbrush, bristle. All you have to do is gently just hold it in indirect contact with the teeth. But I don't find that people do that when they use it, they not only use the rotary but they use it as if it's a manual. And while the bristles are going there, they're doing this with their hands. So you're kind of recapitulating the same thing you do with a manual toothbrush And I find that patients can do a lot more damage with that. So if you're using the rotary toothbrush correctly and just gently letting the bristles and the battery power do the work, then you should be fine. But in my experience, that's not what people do. They tend to be just as aggressive as they would be with the rotary toothbrush as they were with the manual toothbrush. And then it can be quite a problem. That's when we really start to see some gingival recession, because now you're really if you're really brushing hard before you have Pemphigus and getting gingival recession because of an aggressive tooth brushing and now you add in a rotary instrument in addition to what you you'd be applying from your manual can really exacerbate any problems.

Amethyst: Great, Thank you. Is there a good way to practice brushing with just a regular manual toothbrush or maybe one of those sponges?

Dr. Kelsh: Again, it really depends on your disease activity. If you have a mouthful of ulcerations, and oral hygiene is going to be a misery, maybe just rinse with some warm salt water just to prevent a little debridement. That's these little sponges on there, just gently, just to kind of remove surface debris. As you start to improve, then you can increase the level of hygiene that you're going to be able to do. And you're going to self assess. Some people can't do oral hygiene because they're just so miserable. Some people have very high pain tolerance

thresholds and are able to do oral hygiene in spite of oral lesions. That's going to be individualized. It's safe to say the softest possible toothbrush that you can use the most minimal and least caustic toothpaste and then gauge your assessment. And lean your way back as the lesions improve. You can kinda come back up with your oral care products and add back in the things that you're using before you had Pemphigus and Pemphigoid and take it from there.

Amethyst: Great. Thank you. Well, thank you for all the information today, Dr. Kelsh. I would also like to give a huge thank you to everyone on the call for joining us today and thank you to Sanofi Regeneron Genentech, and argenx, for helping to make today's call possible. Before we go, I have a few announcements: Join us for our next IPPF Patient Education Webinar on July 20th with Dr. Praneetha Thulasi to discuss "Eye Care for Pemphigus/Pemphigoid " and answer your questions. You can register online today.

Do you wish there was a better understanding of our diseases by doctors and researchers? Do you wish there were more FDA-approved treatments and better treatments available? Well here's your chance to get involved and make these goals a reality - Join the IPPF Natural History Study today!

The Natural History Study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). Your information is private, the IPPF Natural History Study follows strict government guidelines to assure patient information is protected.

Your participation and the data will be used by the IPPF to help advance research, better understand the patient journey, find better treatments, and hopefully one day a cure. By sharing your journey and answering some questions, you directly have an effect on the future of all people affected by pemphigus and pemphigoid. So get involved today! You can find the Natural History Study by visiting www.pemphigus.iamrare.org

There are many opportunities coming for our community to get involved with research. From clinical trials for potential new medications and online surveys to patient opinion panels, telephone and video interviews, there may be an activity that would be right for you. This is a great opportunity for us - as patients - to really have our voices heard and to be part of scientific research to help others with our disease. Please keep an ear out by signing up for our mailing list to learn more about these opportunities.

Do you want to become a hero in our community and continue to support the free services and support the IPPF provides to you, such as today's webinar, the IPPF's Peer Coaches and our find a doctor map? If so, become a Healing Hero today! Healing Heroes fund the future of the IPPF community by making sustaining, monthly gifts to support our mission of improving the quality of life for all those affected by pemphigus and pemphigoid. No amount is too small even a \$10 or \$15 monthly donation goes a long way and continues to allow us to provide for the greater good of our community.

The IPPF has a number of upcoming virtual support groups across the country. If you are interested in attending a meeting, please check the IPPF's Event Page to register for a meeting.

Also, we are always looking to expand our support network. If you are interested in starting a support group in your region please contact Becky Strong at becky@pemphigus.org. It's easier than it sounds to start a support group and you can help connect others in your area with other patients.

This call recording will be sent out with the survey following this call. Thank you all for joining us.

Once again, thank you all for joining us, and thank you Dr. Kelsh for the wealth of information today.