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ANAL DYSPLASIA SCREENING AND TREATMENT: TO PAP OR NOT TO PAP?

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[video transcript]

00:07
So I am going to fly through some stuff, but if anyone wants me to like linger on anything, let me know, or go back. But I'm going to do a little bit of basic review, and then go through some of the current controversies as well. So yeah, so anal dysplasia screening, to pap or not to pap. And I don't have and no one has any financial relationships or disclosures. And yeah, let's do it.

00:41
So yeah, so first some background. So I think most people who do some HIV primary care have some familiarity with anal cancer, and anal dysplasia screening, and pap smears, and all that kind of stuff. But real quick, so anal cancer, almost all of it is squamous cell carcinoma. So it is a kind of skin cancer that's caused by HPV. Anal cancer, specifically, is almost entirely 16 and 18. Though it is important to note that for HIV positive folks, that this graph is showing, this is a Lancet review article just showing HPV related to anal cancer. So almost all of them test positive for HPV, but then also 16 and 18 as a majority, but for folks who live with HIV, there is this kind of significant sub population that isn't 16 and 18. That's just important to keep in mind, especially when we talk about HPV testing, because some of that is specifically 16 and 18.

01:28
If you've never seen anal cancer here are a few like real world, this is actually one of my patients who I diagnosed. And then so usually late stage anal cancer, but even early stage, this was actually still considered SISCCA, so just superficially invasive, but you can see it's not subtle. So this is like actually poking out, it felt like a nose, like really kind of like cartilaginous like firmness. Same with this, so this is all kind of a very firm kind of feeling. Very ulcerated, very angry looking. But then sometimes, this picture is just to show you that it can also be very subtle. So this is on HRA, so for the high resolution anoscopy, especially when you're diagnosing it early, you would never know it's even there. And actually there was a study showing that 50% of people were asymptomatic when diagnosed on HRA. So sometimes it's obvious, but sometimes it's not, which is why some of this is important for screening.

02:21
So HPV, most people are very familiar. So I call it the common cold of sex, almost everyone gets exposed. As soon as we start touching people we start accumulating HPV, it's probably why it's not quite as effective for those of us over the age of 26 to get the vaccine. And it can also cause worsened condyloma, but those are by definition low grade, so not as concerning for cancer, but they can kind of coexist with high grade lesions. And the other kind of interesting thing, and I think this gets confused a lot, is there still isn't really quite a consensus, even amongst like the HPV gurus. And I'm thinking of like Dr. Palefsky, who's like helped design the HPV vaccine, there isn't really a consensus on whether HPV goes dormant kind of like HSV, or if it's something that your body can actually clear and no longer have productive infection and it's not even living in your body anymore. People kind of go back and forth about whether it's reinfection or if it's more reemergence. And it doesn't matter too much, that's more of an

academic concern than it is, because the other thing is that most people do test positive for HPV when you swab them, especially in HIV positive populations.

03:25
Also, let me know if I'm talking too fast, but I'm just trying to get through stuff. Yeah, so this is kind of the old school view. We used to think of the pathology as a continuum. So you would have normal and then you would go to LSIL, and HPV would slowly then turn into HSIL. But now the new, kind of updated, thinking is that those are actually two different pathways. So either HPV goes down this productive pathway. So HPV really wants to be low grade, so low grade infections are the ones that are more like exophytic. So they're going out into the world, those are the works. There is a ton of HPV being produced in the cells and then getting released. But then something goes wrong sometimes and actually the HPV episome can get integrated into your actual DNA and that's when those oncogenes get turned on, and that's when it transforms into a high grade lesion. So high grade lesions actually isn't a very productive infection, it is not creating much actual functional HPV, so it's not good for HPV either. Not that we need to personify HPV. And then HSIL is the same thing as cancer, it is just whether it's bounded by the basement membrane or not. And so as soon as it goes past the basement membrane, it does turn into cancer. So you'll also see sometimes HSIL being called carcinoma in situ, that can especially be distressing when you see it in a patient's chart, and sometimes even pathology departments will label it as malignant. I've had that happen a few times, and the patient will think that they have cancer, but it's actually still just high grade.

04:52
Yeah, so this is just HPV is almost universal, and this is just a snapshot cross section with a forest plot of many different kind of cross sectional studies. So the prevalence of HPV, so any kind of HPV is 93% in HIV positive MSM, and then for high risk HPV it's 74%. So super high prevalence in the population. And that's at any one moment. So if, you know, if you tested those people over time, you'd probably even have a higher percentage.

05:21
And this is just another question that I get asked and I'd just like to point out. This graph, there's a lot going on in this, but the main point is that there is a lot of anal HPV in cis women as well, and this will get important when we talk about the ANCHOR results. And also it does not, you do not need to have anal sex to get anal HPV. And actually, in some ways, you can see the prevalence for anal HPV is actually higher than cervical HPV in these kind of cross sectional prevalence studies. And it's not because all these women were having anal sex, it's more just we don't know exactly why. But in some ways, HPV really loves the anal canal. And part of that is because it needs that, and there's like one supposition, it needs that kind of access to the basement membrane and because the skin is so thin in the anal canal, it's probably an easier place for it to infect. But it's just conjecture.

06:13
Another question we get asked is whether condoms prevent, this is like another kind of forest plot so a really good kind of like amalgamation of data, and condoms aren't super effective at preventing HIV. Obviously, condoms are great for lots of things. It's great for syphilis, but it's not

so good for HPV. The one thing it is a little bit effective, up at the top here you can see it's kind of broken down, but this is for genital warts. So there's a little bit of efficacy for that, but not quite for the dysplasia.

06:41
So anal cancer. So why are we focusing on this? Why has it been something we've been talking about now for a few decades? And it's definitely been kind of in the air, especially controversial, like what we should do about it. So part of the reason why people are really kind of emphatic and we've been trying to do something about it for so long are a couple things. So first of all, anal cancer is a terrible cancer. It is actually, I compare it to colon cancer here. So in terms of survival rate, it really matters when you find the cancer because the more distanced it is, especially when it's stage four and metastasized, you have only a 30% survival rate versus if you get it early on there's an 80% survival rate. The other unfortunate thing about it is that the standard of care is chemotherapy and radiation. So that is associated with very high morbidity. So most patients do have symptoms after treatment, and 20% of those go on to be chronic symptoms. And I have I think six patients on my panel who have a history of anal cancer, because we see them every six months and for a few of them it's really debilitating, and really sad. And the other really kind of unfortunate thing about anal cancer is the high recurrence rate, so it's up to 20%, which is also why we keep a close eye on people after they've been diagnosed. And then the other thing, and this is more important to the folks who take care of HIV positive patients is that the incidence is just is very high. So you know, I like to use this graph because it kind of breaks it down, especially comparing it to other very common cancers. So prostate cancer is something that, you know, is a little less aggressive, but something that we do screen for sometimes. But I think the better analogy is to colon and rectal cancer. So the incidence is 40 per 100,000 in the general population and in the HIV positive population, it is around that. And we have a whole system, we have the colonoscopies, we have the FIT kits, all that kind of stuff to do screening. And for HIV positive men who have sex with men, the incidence rate is anywhere from 80 to 130. The 80 was the international number from like the Lancet review article, and 130 was actually from NA-ACCORD study. We do think those numbers are real. So the rate, so 130 per 100,000, or about 1 in 1000, what I usually tell people is that you know, that's not horrible. If that's your individual person, 1 in 1000 isn't crazy. But for cancer, that's definitely an imperative and we should be trying to do something about it to lower the rates.

09:01
This is a really, so this slide is also very busy, but I think it's helpful to have just because when we're talking about who should pap and who shouldn't, this is a visual breakdown of the different incidence rates pulled from many different studies to say what the rate of anal cancer is in these specific subpopulations. So the obvious like homerun, definitely we should do something about it, is HIV positive MSM. I think most people are aware of that. When it gets a little bit murky, and that's because of the numbers, are for HIV positive men who have sex with women. So you can see here these cutoffs, it's also really interesting. This slide was part of kind of starting to talk about this specific question of who should we screen. So this lower line is the incidence of 25 per 100,000 and that was what cervical cancer was before we started the entire program of pap smears and colposcopy and LEEP and all that kind of stuff for treatment. So that's kind of. in

some ways, a very kind of direct corresponding illness with the same pathology. But also just kind of intuitively, if you're talking about who you should screen, the burden of disease was the same in the people who are above that line. And then this line up here, so this is the 50 per 100,000 for colon cancer, which we also have this huge cancer prevention program for too. So you can see men who have sex with women, they fall into this kind of more gray area, especially over the age of 30. And then also women. So this is cisgender women, HIV positive, and again, age related, they're right on that line of what cervical cancer burden was before.

10:40
And this is another question that we get asked a lot. So you know, whether HPV in other places makes a difference, and it does, but not the most common. So most people who have dysplasia, it's more cervical dysplasia and cervical cancer. And those are actually lower risk in regards to anal cancer. But the ones that are higher risk, and it kind of makes sense because it kind of shares proximity, is vulvar cancer and vulvar pre cancer, they do correspond to a higher risk for anal cancer. And then finally, there are people who have other kinds of immunosuppression, either because of medications or different autoimmune diseases. And those don't quite fall into the range, but definitely that's an area of active research to kind of see if they would qualify for screening as well.

11:25
So yeah, so this is where we're at. And actually, this is super topical, because actually I was going to update my slides and I realized that they just updated the guidelines two weeks ago, so I had like a little bit of a mad dash to update. So the New York AIDS Institute has published guidelines on anal cytology and anal dysplasia, so all this like screening stuff, since like the early 2000s. And they were really pioneers in recommending this, because of that kind of imperative and that comparison to cervical cancer, and just the astronomical rates of anal cancer in HIV positive men who have sex with men specifically. So they're still kind of like trying to blaze a trail, and they are still publishing guidelines, and there aren't many out in the world, so this is one of the only kind of guidelines. I think there will be more soon because of the ANCHOR results. So that's definitely something to keep in mind is that these are one set of guidelines, but there probably will be more coming soon, especially as this becomes more established as standard of care, which it should.

12:29
So yeah, so the number one, so before we get to pap smears, there's a couple of kind of like obvious recommendations. So vaccinating everyone, there's a little bit of residual benefit up to age 45. I have a slide later, but basically, another question we get asked is whether vaccination is good for secondary prevention. So for someone who has high grade, unfortunately, there was a randomized control trial that came out a couple of years ago that just really shows no benefit at two years. We're still waiting for, there's like a washout period, and there might be more benefit later. But for now, that's not a good reason to give it. So you know, sometimes patients get the vaccine, they think they're going to be cured. And it's just not true, unfortunately. But we do see some residual benefit up to age 45, so obviously, we've expanded that and we recommend vaccination to everyone.

13:18
The other thing that often gets overlooked, especially when doing pap smears. Pap smears are really good and they're meant to screen for dysplasia, so dysplasia are the precancerous lesions that can increase the risk for cancer. But digital anorectal exam is really the screening test for cancer itself. And that's something that every primary care doctor can do themselves. So really performing the DARE annually in folks who are high risk, so most HIV positive folks over the age of 35 really should get an annual digital anorectal exam. And any abnormality, so especially those kind of like firm feeling nodules, sometimes they're tender, sometimes they're not, if you feel anything like that they definitely should be referred. And then finally pap, so pap has kind of been the most kind of back and forth. The New York AIDS Institute has recommended pap smear since the early 2000s, and now they've expanded that too. It used to be just HIV positive men who have sex with men and then like a little bit more individualized for cis women and other gender diverse populations. But really now it is for everyone, they do leave out cis men who have sex with women, that might change. And definitely they still say that you can give it to those folks who so ask for it. I'm sorry, I feel like this is like a little bit of a typo, but we're not looking for potentially cancerous cytologic abnormalities, the pap smear is really more about dysplastic not neoplastic findings. But yeah, and I think that might change and you know, the main kind of governing, my like kind of go to for this kind of information, is the International Anal Neoplasia Society or IANS, and they're just starting to meet to come up with their own guidelines. And I wouldn't be surprised if they have a statement on men who have sex with women, especially because there is some incidence of anal cancer. So we'll see.

15:13
Yeah, and then basically, so you do a pap smear, it comes back. And if it is anything other than benign, it was that you'd send to HRA. These brand new guidelines that came out last week are now recommending HPV testing and I would just say that this is, we'll get into it a little bit, but it's still kind of controversial, and we're not quite sure what HPV testing and what role it's going to play, and there probably gonna be differences of opinion. But at baseline, we want to refer anyone who has an abnormal pap smear to HRA, they're saying specifically for the lowest level of abnormality, which is ASC-US, and which plenty come back as ASC-US. If you do a reflex HPV test, or you do an HPV test with the next sitting that you could maybe skip the HRA, and I'll show you the rationale behind that.

16:06
Just real quick, what is HRA? So I think most people have heard of this or seen it. But this is my setup, I actually did one this morning. And we just use a colposcope, and we do a magnified view of the anal canal, and use acetic acid and iodine. And we're looking for those dysplastic lesions, it only takes a few minutes. And we do very small biopsies, this is actually different from the colposcopy, we don't use Tishlers, we use Baby Tishlers. So it's a very small bite. But there is bleeding and pain afterwards, it should be pretty minimal. And then any confirmed HSIL is treated. And this is what it looks like. So we're looking for these acetowhite lesions. So this is the squamocolumnar junctions, that's where the skin ends on the inside of the body. And the main thing we're looking for are these acetowhite thickenings. So this is, like you can't really tell because it's a 2D image, but this would be a little bit kind of raised in my scope. And you can see very kind of subtly these like little course punctations, so some vascular changes. And then

when you stain with iodine it turns bright yellow, because it can't take up the dye because of the dysplastic changes, and so that's an obvious HSIL lesion.

17:10
Yeah, so this is me just saying like, okay, so they're adding this HPV testing. And I think the reason, the main reason for this is in some ways is rationing care. So there isn't HRA available in many places. So trying to figure out who, so doing as much risk stratification as possible is not a bad idea. But there is a couple of complications. So first of all, this is the sensitivity and specificity of pap smears. So the main one is this, you know, so folks who are living with HIV it's pretty sensitive, so 80% sensitive and only 54%, so all of these suffer from a low specificity. And we want to get things, for a screening test, we want the sensitivity to be as high as possible to really dial in on that higher negative predictive value and not miss anyone who could possibly have high grade, especially because the burden of disease is so high. And this is just the same one, but they have similar results. So cytology, so 81% and 54%. And then versus high risk HPV, so you get that big boost, well, not a big boost, but you go from 80% to 90% sensitivity. So you capture more and have less false negatives, but at the expense of you're going to have a lot more folks who come in who maybe don't have high grade lesions. And those are pretty much the same results. So these are two different meta analyses.

18:32
Yeah, and then things get really, to be transparent, like a little messy and also a little bit confusing for what do you do after someone had high grade or had a low grade biopsy. And basically, there are going to be, we're still trying to figure that out I would say, and it is kind of different for different facilities. And I'll show you what ANCHOR did, and I'll show you what I do.

18:58
But I think just at baseline, the reason for that messiness, and the reason for that is that there are a couple of different kinds of competing needs and goals and realities with all of this. And the first thing, so I'm going to go through each of them and show you a little evidence for them. But first of all, the prevalence of dysplasia is incredibly high in high risk populations. So if you go looking for dysplasia in HIV positive men who have sex with men, but even cis women and also cis men who have sex with women, and then also trans feminine populations, the dysplastic burning is going to be pretty high. And so because of that, any screening test we do, we want to have a low threshold to have people come in for HRA because we know like there is some argument to say that we need to do HRA on everyone because the burden is so high. But because of that kind of like need to ration a little bit, there should be some screening tests, but that screening test should have lowest threshold as possible. Which is unlike cervical cytology, where you kind of like base it if it is ASC-US, or LSIL, or HSIL, and then who gets a colposcopy after that. We send everyone with any kind of abnormality. And so there is that trying to to use high risk HPV to nuance that a little bit, but that's a little controversial. And the other kind of tricky thing, and especially trying to review literature and talk about HRA evidence, is that HRA is the gold standard for finding dysplastic lesions. So that's the best way to find them. There is no other test that like has a better kind of capture rate and kind of confirmation. But unfortunately, it still has a sizeable false negative rate and a very high inter-operator variability. So most people say, who do HRA, they will tell you that it's not an easy procedure to do. And

the learning curve really is about 10 years long. So I've been doing it for six years now, so I'm not even considered like a veteran yet. But I'll show you an example of that. So these are actually two studies from like, kind of, they're considered the titans in the field. So this is from Palefsky back in 1993, and this is a busy slide, but the main important thing is just how much highgrade he found. This is more kind of like a proof of concept study that he did, showing that you could find highgrade in anal biopsies. And the percentage so only, you know, based on the pap smear, so you can see normal, ASC-US, LSIL, and HSIL biopsies, and right now standard of care for HSIL pap smears you should find an HSIL biopsy 90% of time, and back then they only found it in 42%. And then these numbers are just insane. It's only a 4% rate in LSIL and 2% rate in ASC-US. So a more recent study, and it's a considered one of the more premier studies, so this is from SPANC, they do have a good sense of humor for naming these studies. This is the main study in Australia, and in SPANC this is one of the main outcomes that they saw, because that was a monitoring study to kind of see like what the rates of highgrade were in different populations. And you can see based on the different cytology outcomes, so ASC-US, LSIL, ASC-H and HSIL, much higher rates of HSIL. So this is in I think 2017, as opposed to 1993. So even just the field has evolved and now we just have a much higher standard of how much HSIL we expect to find in these high risk populations. And if you look at a paper and you see lower numbers, more like this 1%, 2%, or even like 10%, it just makes everyone kind of question whether that study is valid or not. So just something interesting to know.

22:34
And then the other unfortunate thing is that there's a very high recurrence rate for HSIL. So ongoing monitoring is essential for those with known HSIL. So this part of the guidelines is trying to figure out how to keep an eye on people who have been now diagnosed with a high grade lesion, and whether we can let them go and go back to cytology, or if we need to kind of keep an eye on them. And this is just from a recent study showing the recurrence rate. This is actually Michael Gaisa at Mount Sinai, and he did a great study that showed that at three years there's a 70% recurrence rate, and at one year there's a 50% recurrence rate. So recurrence, and anyone who does HRA would tell you the same thing, that recurrence is really the rule and not the exception. Interestingly enough, that's also true for cervical pathology in folks who live with HIV. So like the reason that people are vulnerable to this, who live with HIV, is specifically because the body has a hard time kind of keeping it under control. But it's also probably because HRA is a difficult procedure, we don't always do complete treatment. Yeah.

23:36
And then to the last piece that I mentioned before, so capacity is limited. I'm sure some of you even experienced that. So it's frustrating because you do a pap, and then what do you do with it? And if you only have access to like one person we can do it and like the next appointment is six months out, then you really need to kind of ration the care a bit. And that can be kind of in conflict with like all these other needs that I talked about. And we even at Callen-Lorde, we have three HRA providers now. And my next available is like two and a half months out. So even we struggle, even just within Callen-Lorde, we struggled to keep up with demand.

24:11

Yeah, and then also why high monitoring? And the other reason for high monitoring, other than the high recurrence rate, is that the other kind of like main thing we worry about is persistence of HPV infection and these high grade lesions. So the five year risk of anal cancer, so this is going to be updated with the ANCHOR results, but there's a pretty high conversion rate. These are all like cohort studies so none of them are great, which is why we're really looking forward to the ANCHOR results which have a better idea of these conversion rates of high grade to cancer. But as you can see, relatively high.

24:40
Yeah, and so this is the full flow sheet for the New York AIDS Institute. So this is the new ASC-US testing and then they're saying if you have a low grade biopsy, you need to come in every year for HRA until it's normal for two times. So it's trying to like balance both like the idea of persistence and concern for HPV activity over many years and having a higher level of watching them versus needing to conserve HRA. And HSIL is a follow up at six months. And that's similar, so this is our guidelines, I'm not going to go into it in detail. But basically the way I broke it down is a similar kind of idea trying to risk stratify for low, medium, and high. So people who have normal cytology get to do a yearly pap. So folks who have LSIL, and my kind of rationale for using high risk HPV testing is actually more to rule people out of being high risk instead of ruling people in to screening. And part of that is because if you're doing annual cytology, I feel like that's already boosting sensitivity to a certain degree, whereas we are really trying to look for people who are lower risk and can get out of this loop of needing HRA so frequently, and we can kind of de-escalate the screening. So I use high risk HPV testing to get people out of the HRA cycle. So if they're negative for high risk HPV and they have benign pathology, they would go back to cytology. Otherwise, they would go to annual HRA. And then finally, the people who are high risk, it makes sense, are people who have diagnosed high grade and they go to the treatment pathway, and this is also divided. So people who have high grade and get treated and it goes back to being totally normal, and this happens very infrequently unfortunately, but people who go back to totally normal, so having a normal biopsy and negative high risk HPV testing after two HRAs, will be able to go back to cytology. Otherwise, most people get stuck in this loop where they have high grade over and over again and they come in every six months, or they have either low grade or the high risk HPV positivity persistence, and they go to yearly monitoring.

26:31
So yeah, so that's a lot. And I think it's continued to be a lot. And you know at this point, we have the ASCCO app to do risk stratification for colposcopy and I wouldn't be surprised if it's sometime down the road to get the same thing for anal. But for now, I totally acknowledge that it is confusing, there are probably going to be multiple guidelines coming out in the next few years because of the confirmation that it is an effective treatment. But what I would say for most primary care providers, like the simplified guidelines I would say are to do an annual DARE. If you're not sure, or patient hasn't had anything in a while, just do that pap smear and then don't worry too much about the HPV testing. And if it's just anything other than benign, having them go see an anoscopist. I mean, if anything that anoscopist can then apply whatever guidelines they're using, and they can do their own risk stratification. So that's my takeaway.

27:25
Yeah, so that ANCHOR study. So I think most people know this too. So the ANCHOR study, was this huge NIH funded, very exciting, multicenter study, looking at the efficacy of HRA to prevent anal cancer. It also has a quality of life aspect, which I'm super interested in, because it is a huge kind of array of people's responses. So some people it's the worst thing in the world and they never want to do it again, some people it's not a big deal and they take a nap while I do it. But then the other thing is, it is going to be this wonderful kind of bank of data that we can then use to look at the natural history of HPV, which isn't just applying to anal cancer, but just HPV natural history. We won't ever have this opportunity again, probably. So they're definitely gonna use all those samples. And even though the trial is now ended, yay, because of the high success rate, they're still going to continue to monitor those patients and continue to collect those samples to continue to get that kind of repository of information.

28:26
So and the other very recent thing. So Dr. Palefsky is like the rockstar, he's like spearheaded most of this information. He's the one who designed the HPV vaccine or helped to do that. I think he's amazing. But he presented a CROI, I think it was last week or two weeks ago, and finally gave some specific information. So this announcement came out in October. And now in February, we're getting the actual number. So 50%, it was a 57% reduction in risk, so that's relative risk. And so of the other things that are very interesting about with the numbers that came out, so 10,000 were screened, and talking about that like high burden, 50% had HSIL. So it varied a little bit between cis male, cis women and trans feminine folks, but it was basically like 45 to 60%. And they had a much higher burden in the cis women than they were expecting, actually. And they also had a much higher burden of cancer than they were expecting as well. So 9 versus 21, so that was that 57% reduction in risk. And so the incidence correspondence in that old slide, showing the NA-ACCORD incidence, but the highest number we ever had was 130 per 100,000. So this 173 per 100,000 or 402 per 100,000 is just astonishing. I think it does speak to there probably was some selection bias in the studies. So people who were sent to the ANCHOR study probably are at a higher risk than the general population, but it's still a good demonstration of efficacy.

30:01
So in terms of like the ANCHOR study, right, so like now we have this like very validated wonderful data that it absolutely works, it absolutely reduces the risk of cancer. What was their protocol? And their protocol was actually incredibly strict. And it was no matter what, every six months HRA. So that's higher, that is way higher monitoring than, so even if they had benign results they would still come in for HRA every six months. So obviously, that's a much higher standard of care than what's being proposed by the New York AIDS Institutre, which is why I think there's going to be now a lot of back and forth about what the appropriate level is going to be for the general population moving forward.

30:41
So yeah, and if you're interested in this, like we need more people. So now that like the floodgates are getting opened, and this is going to become like, it has now become the standard of care emphatically and insurance is probably going to start covering it more. We're gonna

need people to do it. So the main pathway, and the best pathway in my opinion, is to do the IANS training course. The other very exciting thing is that the scientific meetings, that's like the main kind of like meeting of the minds for people who are making these guidelines and doing this work, is going to be in New York this year. It was in Amsterdam in 2019, that was last time we met in person. It's my favorite. I mean, I'm biased, but it's my favorite meeting, I love this group of clinicians. So you can come this June, I highly recommend it.

31:23
So I'm sorry. I think that's all the time, but if anyone has any quick questions, I would love to hear it. I hope that was helpful.

[End]