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Expert Interviews

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Implementation of the New HHS Anal Cancer Screening Guidelines

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Dr. Jeff Schouten, UW faculty in Surgery and in Allergy and Infectious Diseases as well as ANCHOR trial co-investigator, discusses the new anal cancer screening guidelines for persons with HIV then focuses on implementation barriers and considerations for integrating the new recommendations into HIV primary care clinical practice.

Topics:

- OIs and HIV
- anal cancer
- HSIL
- HPV

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introduction**[00:00] Introduction**

Hello, everyone. I'm Dr. Brian Wood from the University of Washington in Seattle. Welcome to the National HIV Curriculum Podcast. This podcast is intended for health care professionals who are interested in learning more about the diagnosis, management, and prevention of HIV.

As background for today's discussion, the prevalence of HPV [human papillomavirus] infection, anal dysplasia, and also anal cancer are higher in persons with HIV as compared to persons without HIV. In addition, the incidence of anal cancer and the mortality rate from anal cancer are rising for people with HIV in the United States. For the first time, the Opportunistic Infection guidelines, which were developed by the NIH [National Institutes of Health], CDC [Centers for Disease Control and Prevention], and HIV Medicine Association (HIVMA), now include a section on anal cancer screening. The release of this new guideline was long-awaited, but clinics will likely face challenges implementing the new recommendations.

Today, I am lucky to be joined by an expert on this topic to discuss the new guideline recommendations as well as practical considerations for implementing them. Dr. Jeff Schouten is an Emeritus Clinical Associate Professor of both surgery and allergy and infectious diseases here at University of Washington. He also serves as head of the Anal Dysplasia Clinic at Madison Clinic, our Ryan White-funded academic HIV primary care clinic. He is former director of the Office of HIV/AIDS Network Coordination at Fred Hutchinson Cancer Center, and he was a co-investigator of the ANCHOR [Anal Cancer/HSIL Outcomes Research] trial, a pivotal trial that will be a part of our conversation today. Welcome, Jeff.

Dr. Schouten

Good morning. Happy to be here.

anchor-trial-key-points**[01:37] ANCHOR Trial Key Points**

Dr. Wood

So, Jeff, really honored to have you, and I think this is a really important discussion. And you were a co-investigator of the ANCHOR trial, a very critical and influential trial, as I mentioned. To start, would you summarize for listeners what you see as the most important take-home messages from that study?

Dr. Schouten

This was a study looking at whether or not we can prevent invasive anal cancer developing in people who are

living with HIV, who are at much greater risk than the general population, and men who have sex with men who are increased risk, but not nearly as much when HIV is in the mix. There had been a lot of debate about that. In fact, the Society of Colorectal Surgeons didn't think there was any value in treating these precancerous lesions.

So, we had a wonderful 4,500 volunteers who got randomized to one of two approaches, being monitoring or no treatment, or treatment, which is ablation. And we can talk more about what is involved with that. We showed for the first time that we decreased the risk of anal cancer in people living with HIV with an ablation office space by 57% decrease. So, a pivotal study that, as we'll talk about, has already resulted in guideline changes.

Dr. Wood

Absolutely. Thank you, Jeff. So most important take-home message from that study for listeners, if I heard you correctly, we finally do have data that identification and treatment, eradication of anal HSIL [high-grade squamous intraepithelial lesion] has high efficacy; not 100%, but high efficacy at preventing anal cancer. Is that correct?

Dr. Schouten

Correct. And these are all HPV-driven cancers in the anal canal.

Dr. Wood

Thanks for adding that. So, as you mentioned, that was very influential on new guidelines, which are finally available. They were long-awaited, highly anticipated, I would say.

anal-cancer-prevalence**[03:19] Anal Cancer Prevalence**

So, let's turn to talking about those guidelines. And maybe, Jeff, you can add some perspective on why it was important to develop national guidelines for anal cancer screening.

Dr. Schouten

So a couple of key points. There were quite a few people who didn't think that we would make an impact on incidents of invasive anal cancer. For many reasons, this disease, even though it's HPV-driven, the same strains of HPV associated with cervical, vulvar, vaginal cancer, it behaves very different in the anal canal. And there's a much higher recurrence rate. It's much more difficult to ablate the disease in the anal canal. Re-treatments are much more common than with cervical dysplasia. So, for those reasons, a lot of people felt like it wouldn't be beneficial to treat these precancerous lesions; you wouldn't impact invasive cancer. But in fact, we did, significantly.

The other really critical thing, though, as we talk about the guidelines implementation, we found a very high rate of anal cancer in the ANCHOR study, twice of what the study was designed. So, the study was designed to show a reduction in anal cancer rate of over 50%, with the expectation that cancer in the active monitoring group would be about 200 cases per 100,000 person-years, versus lowering that by 50% to 100 or less per 100,000 person-years. We actually found double the incidence in both groups. So, while we did reduce the incidence by 57%, we had an incidence of nearly 400 per 100,000 in the monitoring arm and 200 per 100,000 in the treatment arm. So, we can talk more about treatment needs, but this showed this is as big a problem as we feared it was in people living with HIV, or even greater, in this well-conducted national study.

Dr. Wood

Thanks, Jeff, for emphasizing that. Do you have speculations on why the incidence was so much higher than

expected, double than expected?

Dr. Schouten

Well, I think this was a very detailed follow-up of these persons. Now, granted, all of these cancers would have been clinically significant at some point if they were not in this study. But we did find some early cancers, what's called superficially invasive squamous cell cancers (or SISCCs), but those definitely would've developed into more obvious cancers over time. So, we did diagnose cancer early in this study. Everyone was seen every six months, which is important to note. And I think it was a good spectrum, though, of people living with HIV. We did have a lot of long-term survivors so I think that we could talk about risk factors as we triage who we should be screening, but older age, longer duration of HIV infection, lower nadir are all correlated with increased risk of anal cancer. And that was the predominant group of people who we enrolled in ANCHOR.

Dr. Wood

That seems like a really important point. An overall message here for listeners: I think anal cancer is highly prevalent for people with HIV, and it is really important to screen, and we finally have guidelines, which we will talk about next. And as you said, the incidence was even higher than predicted. I've also heard you say in the past that the incidence has been rising. And I believe that mortality from anal cancer has been rising for people with HIV as well. Do I remember that correctly?

Dr. Schouten

Correct, yes.

screening-recs**[06:25] Screening Recs**

Dr. Wood

Overall message, screening is very important. So, let's dive into what is included in the new guidelines, which can be found in the HPV section of the opportunistic infection guidelines. So, I'm just going to start with the first screening recommendation, which is ask everyone with HIV about symptoms every year. Can you add some insights for listeners and clinicians about what symptoms they should ask about?

Dr. Schouten

I think it’s two important points. HSIL is always—high-grade squamous inter-epithelial lesions—are always asymptomatic. So, when we talk about symptoms, we're actually addressing what cancer is presenting with symptoms, not HSIL. I think that's an important point. And the ANCHOR study was not a screening study. All comers went to HRA [high-resolution anoscopy] directly, so we don't have a lot of data on screening methodologies and the best approach to screening from ANCHOR. We will have some more information over the next couple of years in secondary publications, but it was not a screening study.

So, these recommendations that came out from the CDC and also the recommendations that we'll talk about from the International Anal Neoplasia Society (or IANS) just kind of coming up with screening recommendations in a fairly data-free zone; not completely, but not from any randomized clinical trials. But basically, the approach is to triage people who are symptomatic or have an abnormal digital anorectal exam, what we call a DARE. We can talk about that, why we don't just call it a rectal exam. But the symptom screening and the DARE screening is to identify anyone with a possible prevalent anal cancer. And those should go directly to evaluation if HRA is available, or to general surgeons for anoscopy, if it's not available.

But for screening for HSIL, we're talking about asymptomatic lesions that we find there. So, the symptoms with anal cancer tend to be significant anal pain. What I always tell my patients, any anal bleeding that lasts

more than a month, significant anal pain more than two weeks or three weeks, or a mass or a lump that you can feel that doesn't go away like a hemorrhoid would in a couple of weeks, those are the kind of symptoms you should go to your provider and then talk about.

Dr. Wood

I see. So, inquiring about symptoms is really screening for any symptoms of anal cancer that is prevalent, and then we'll talk about screening for asymptomatic HSIL in a bit. I appreciate you clarifying that.

when-to-start-screening**[08:54] When to Start Screening?**

Dr. Wood

So, if I can ask a follow-up question. My interpretation of the guidelines is we as clinicians should be asking about this to everyone regardless of any history of anal intercourse. Is that correct? And can you help me and listeners understand why?

Dr. Schouten

So, one thing I would really emphasize: receptive anal intercourse is not necessary to have anal cancer. I see a lot of people who have anal cancer who have never had receptive anal intercourse. It's a field defect in sense of once HPV is present in the anogenital region, it can either go into the vagina, vaginal tissues, vulva tissue, or cervix, or into the anal canal. The virus likes to be in warm, moist skin. And it's a skin infection. It's not a mucous membrane infection. So, it's that transitional skin in both the cervix and the anal canal where HPV really likes to live. So, it's those areas.

So sexual history, it's true that men who have sex with men are at increased risk for persistent, high-risk HPV and anal cancer, but it's not a good screening approach just to screen people who have a history of anal sex. It is age-associated, risk proportionate to age. It's not a bimodal curve. As you get older, particularly in your 50s, 60s, 70s decades, your risk of anal cancer increases. In the general population, it's a pretty rare cancer, one to two per 100,000. But like I said, we had an incidence up to 400 per 100,000 in the ANCHOR study.

And so, it is age-related. Both the IANS and the CDC guidelines draw some lines at age 35 and above and 45 and above, looking at when to start screening. You know, someone who's 21-year-old with a high-risk HSIL lesion, that's probably going to be gone by the time they're 30, 35. We’re way overtreating. Oftentimes, the immune system just clears those infections in younger people.

Dr. Wood

I see. I think those are really important clinical points.

screening-challenges**[10:46] Screening Challenges**

Dr. Wood

Let's turn to the next part of the guidelines, which gets to some of the aspects of age and screening that you were just talking about. So, the next part of the guideline states that for men who have sex with men, who are under age 35, and all others who are under age 45 who have symptoms should undergo DARE, as you mentioned, digital anorectal exam, as well as standard anoscopy, not high-resolution anoscopy, but standard anoscopy, which can be done in the clinic. But I want to ask you, what do you see as the major challenges to implementing this part of the guidelines?

Dr. Schouten

I think it's willingness of the patient and the education required to inform people of their risk for anal cancer. You know, I see so many notes of patients referred to me for abnormal lesions of things, and it says, "Rectal exam deferred." And I always have to ask who deferred it: the provider, or the patient, or both? But this is a real hurdle. There's so much that a primary care provider has to do in their semi-annual HIV visits now that this is one more thing that's going to be a difficult procedure to incorporate, both because of patient resistance, the lack of appreciation of the risk of anal cancer, and just the embarrassment of it. A lot of people just say, "Well, I'm not clean, I'm not ready for this today," whatever. So, it's going to take some education for patients to accept a screening approach here for something that most providers haven't talked to them much about in the past.

Dr. Wood

You know, Jeff, I'm identifying with that as an HIV primary care clinician. I've been bringing this up in conversation with patients. And I've experienced that some patients have thought about this issue, are ready, are willing, and others have definitely been more reluctant, and they've never heard about this issue before. They've never heard about anal cancer screening or the risks or the importance of doing it. Plus, our time for visits is very limited, and there's a lot to try to incorporate, so I can identify with all of those challenges you mentioned.

counseling-tips**[12:41] Counseling Tips**

Dr. Wood

As a follow-up to that, what do you think will be most important in terms of patient education, or how might that counseling look? If you were in clinic, counseling a patient about the importance of this, what might you say to them?

Dr. Schouten

Well, I would use the analogy that we do with colonoscopy, I think, or cervical dysplasia screening. These are asymptomatic lesions that can cause cancer. And oftentimes, it's an advanced diagnosis when symptoms present to make it evident there's a cancer going on. So, this is preventative care, just like we do with mammograms, colonoscopy, and so forth. We're screening. We're treating lesions before they become a problem. Even though most of them will never turn into cancer and the risk of cancer is relatively low, it's still too high not to screen for and prevent now that we know we can prevent. And it's normal to be embarrassed and not want to have a rectal exam done. We understand that. But this is a critical part of the procedure, is both doing a Pap smear, which doesn't hurt very much, and doing a digital rectal exam. And then depending on those results, we can determine whether we need further investigations.

Dr. Wood

Thanks, Jeff. I appreciate the way you outlined that.

hra-challenges**[13:50] HRA Challenges**

Dr. Wood

So, let's turn to the next recommendation in the guidelines, which really hinges on the availability of high-resolution anoscopy, or HRA. Can you give us your sense of current HRA availability in the United States and tell us a bit about what it takes to become proficient in HRA?

Dr. Schouten

There's very, very limited capacity for HRA anywhere in the country, even in the couple of centers that did the ANCHOR study, where there may be a little more capacity. In Seattle, we have three or four providers who do HRA. We have no one in the outlying regions in the suburban Eastern Washington, Alaska, so forth - even in places like San Francisco, where they have a large anal dysplasia clinic. There's not the capacity to start screening all men living with HIV age 35 and over, for example.

So, in the ANCHOR study, we projected that we were going to screen 17,000 people to enroll 5,000 people. We thought there would be a one-third yield rate on finding high-grade. We actually found that 50% of people screened had high-grade dysplasia. These were all comers, people living with HIV age 35 and over. And this was not a group enriched with known history of HSIL, which some people thought it might be. It's not.

So, if you look at a large clinic, 50% of people living with HIV age 35 and over, that's a very, very large number of HRA providers and slots that you'd need to do this. There are many cities where there's no HRA even available anywhere. Part of the challenge is really who's going to take ownership at this point right now. And I'm a general surgeon, a surgical oncologist by training. I've also done primary HIV care, so I appreciate the spectrum of people doing this. A lot of these clinics were set up within HIV clinics and had non-physician providers trained, either PAs [physician assistants] or NPs [nurse practitioners], to do this. That model won't work in the general population. Those clinics would not even be able to screen everyone within their own clinic if we were really implementing this at scale.

So, there's no one around in the country who's adequately prepared to embark on this, nor is there any specialist that's going to take ownership of this. General surgeons aren't very interested in taking ownership of this, in part because the reimbursement rate is very low. The RVU [Relative Value Unit] reimbursement set by Medicare is so low that most surgeons will not give up a day in the operating room to come do a day in the HRA suite, for example. And likewise, GI [gastroenterologists] physicians aren't going to endorse this. They can do many more colonoscopies than they can do an HRA exam. And there are some internists who are training or training PAs or NPs within their practice. There's a few gynecologists who are ANCHOR investigators. So, our ANCHOR investigator meeting was interesting because there were a few general surgeons, internists, infectious disease, GI docs, a few gynecologists, quite a spectrum of people.

But where are you going to bring training up to scale with no organization taking ownership? There's no national certification process. There's no board certification process for this or specialist certificate. But the needs are tremendous, the training needs, the experience that's necessary, the equipment needs, the care coordination with an experienced care coordinator. And we need prior authorization. We can talk more about insurance challenges. You need pathology support. You really need to educate your pathologists and have them learn the LAGST recommendations, which are a set of Lower AnoGenital Squamous Terminology recommendations that came out in 2012, which adopted the HSIL, LSIL [low-grade squamous cell intraepithelial lesion] terminology, applying to all anogenital sites.

You need a general surgeon's support because some of these patients that are not going to be able to be addressed in clinic, they're going to need to go to the OR [operating room] for EUAs [exam under anesthesia] and so forth. So, you need a general surgeon that you have a rapport with and a relationship with. And then you'll need patient education materials, as we talked about. This is new to a lot of patients and new to a lot of providers, both in terms of doing a DARE and anal cytology, but also what an HRA exam involves. And I find many patients come to see me and don't really have any idea what they're expecting that day. Some think that they're having a colonoscopy. So, I think that creating patient education materials would be important too.

Dr. Wood

So, I heard a lot of challenges integrated into those comments, including no one specialty really taking charge. And it sounds like even for centers that have an HRA-trained and proficient provider, those individuals may quickly become overwhelmed with referrals because the prevalence of HSIL is so high. So, we can come back in a little bit and maybe talk about potential ways to approach that challenge. It also sounds like there

are a lot of resources and there's a lot of planning and preparation needed before starting this process.

prioritizing-hra-referrals**[18:45] Prioritizing HRA Referrals**

Dr. Wood

Let's turn, Jeff, if I may, to the next part of the guidelines. And let's take for clinics that do have an HRA-trained provider, someone who is proficient at it, has gone through training, is experienced, has done a lot of their procedures. So, in that setting, the guidelines state that for men who have sex with men, and all others who are older than 45 years of age, clinicians should inquire about symptoms, collect specimens for cytology, ideally also HPV cotesting, then perform DARE and then refer for HRA for any abnormalities.

You've just mentioned some of the barriers to implementing that, a lot of resources needed, limited specialists who are trained, the need for more specialists to train for HRA. So, what if a clinic is set up for all of that, but their HRA specialist quickly becomes overwhelmed with referrals, or there's just so many people being screened and being referred? I'm wondering if there are ways for clinics and clinicians to prioritize referrals, or what other approaches you would suggest to manage what could quickly become an overwhelmed specialist?

Dr. Schouten

I think that all of us are struggling with that important issue right now. In terms of training requirements, I should note that the University of California, San Francisco, in conjunction with the International Anal Neoplasia Society, does provide courses in HRA. They're didactic. They're not hands-on. That's one of the problems is, it's easier to get the training for didactic training, but very hard to find where you can do hands-on training; nowhere really where you can go somewhere and actually do supervised HRAs. No institutions will allow that, nor will our institution, of outside providers.

But, you know, everyone is making this balancing act. And the International Anal Neoplasia Society guidelines that were published in May of 2024 have a great table. Their Table 1 looks at the different risk of anal cancer by population, including MSM, women with HIV, MSW (men who have sex with women), MSM without HIV, and so forth. And they drew a line, decided that they were going to have the highest risk category, they're going to define as people with a tenfold increased risk of anal cancer over the general population and add solid organ transplants and history of vulva cancer to that. So those are the groups that they say start with that. So, I think that's a good guideline.

Then there's a second category they call the Risk Category B versus the [Risk Category] A one, where the risk—it’s up to tenfold but not over tenfold risk. And that includes women with cervical and vaginal HSIL, who are not as high a risk for anal cancer as you might think they are. With vulva HSIL, the risk for anal cancer goes up even more. But there's kind of an intermediate risk group. So, I think most people are focusing on that tenfold higher-risk group to start with.

And the other important thing: ANCHOR study was people living with HIV. We do think the same findings would probably apply to other immunocompromised people. There's a lot of people on immunosuppressed therapy. We see a fair number of people with significant dysplasia who are solid organ transplants and bone marrow transplants in my practice. So even though we're at a Ryan White clinic, we see a lot of people without HIV in my practice, but that's another group to think about as well.

Dr. Wood

So, Jeff, making sure I understand that, so sounds like for centers that are set up for HRA but maybe have limited access, so there is an HRA referral, but limited access, you've mentioned prioritizing individuals with symptoms, prioritizing individuals with concerning abnormalities on DARE or on standard anoscopy. And now, it seems like there are some parts of the medical history, and we can provide a link to that table in the IANS

guidelines, there are some other parts of the clinical history that might help clinicians to prioritize who should be screened and referred. Is that correct?

Dr. Schouten

Correct. And the other thing I should note, that IANS also has published a really good paper on training recommendations and credentialing recommendations for certifying someone to be an anoscopist, what kind of criteria.

Dr. Wood

That's great. We can provide a link to that too.

becoming-hra-proficient**[23:00] Becoming HRA Proficient**

Dr. Wood

Do you want to provide just a little more detail on what it takes to become proficient in HRA? You've mentioned a little bit about the difficulty of finding ways to do supervised procedures and sort of get the practice in. Can you just add a little more detail for listeners about what it takes and what someone who's interested in becoming trained and proficient in HRA might seek out?

Dr. Schouten

I think it's much more straightforward and easier once you find the providers who are interested and the funding support for them, which are other big questions. If you're at an institution that already has someone trained to do HRA, you then can go observe. I have people come and observe me for four full days, require them to take the IANS HRA course, the didactic course, which is offered virtual now. And then after observing at least four full days, then I observe them doing and help them do a few procedures. And if I sign off on three procedures that they're competent on then they can start doing them on their own. Usually, have people start doing exams and biopsies and not ablations until they get comfortable finding the HSIL.

Since the ANCHOR study was a once-in-a-lifetime opportunity to randomize people and see if we really made a difference, it was over an $80 million study funded by the NCI [National Cancer Institute], that study was never going to happen again. So, the QA [quality assurance] and the training requirements for that were quite onerous, including in-person observer watching you do a full day of procedures and ablations at every site. And that would never be able to be done at scale.

So, I think that this is the challenge. So, if you're not at an institution where you have an opportunity to train with someone who's already certified, it's really difficult. You can go to another institution and observe. We have some observers coming in. But, you know, once you start doing them, it becomes very clear you need someone over your shoulder the first couple. And as Naomi Jay, one of the heads of the QA committee for the ANCHOR study, said, "It's certainly not see one, do one, teach one. It's see 50, do another 50, and then get certified when you've got 100 under your belt."

So, ANCHOR required at least a patient log of over 25 patient exams looking for the fact that, did you find the HSIL and did you find all of it? So, one of the big challenges at ANCHOR we really emphasize is we needed to ablate all the HSIL, because if we weren't ablating all of it, the approach might've failed. So, it was really an aggressive training supervision process since we wanted to be sure that if we were going to treat HSIL, we treated all of it to really answer this question definitively as we did.

Dr. Wood

That's really helpful to know, Jeff.

no-referral-hra-specialist**[25:30] No Referral HRA Specialist?**

Dr. Wood

And another point from the guidelines that I think I've heard you make is that if clinicians and clinics do not yet have a referral HRA specialist, they should not yet be performing the anal cytology and cotesting. Do I understand that correctly?

Dr. Schouten

Yes, because half of people in ANCHOR had HSIL, and an additional number of those had abnormal cytologies. We collected the cytology, and we can talk about HPV testing because the ANCHOR hasn't run the HPV data yet, and we'll talk about that maybe, but there's no point in identifying something if you can't refer for appropriate follow-up; I don't think. I just think that causes a lot of anxiety. It causes a relationship challenge between the provider and the patient and the institution and the patient. And there are no real avenues to refer outside for this. The institutions that are doing this are pretty much at capacity already, so finding an outside referral is not much of an option here either.

cytology-collection-how-to**[26:28] Cytology Collection How To**

Dr. Wood

Let's stick on that topic and on the setting of someone who does have access to a referral specialist, and let's talk about the cytology and cotesting. So again, this is the setting where a clinic *does* have capacity to refer to HRA. What pearls and words of wisdom do you have for clinicians for collecting the cytology and the HPV cotesting, if available, and then interpreting those results?

Dr. Schouten

So, a couple of things. The cytology has to be collected with a Dacron or polyester, tap water-moistened swab. You can't put lubricant in the canal. It won't collect. It will interfere with cell collections. And the thin prep solution that you send the cells in, if it has lubricant in it, is not usable. So, the first step is always doing the anal cytology collection first, and that's with a Dacron-moistened polyester, tap water-moistened swab.

You gently insert it into the anal canal. You go in about two inches. You can feel it pass through the internal sphincter, which is about where the transition zone is, a little bit above that. So, you want to go a little further than that. And then, just in a sweeping motion, sweeping the sides of the canal and just slowly withdrawing it; on a count of ten, is how slow you're withdrawing it, and sweep around the anal verge also as you're bringing it out. And then you vigorously shake that swab in the thin prep for 20 seconds. I count to myself for 20 seconds. Then, discard the swab. You don't send the swab with the solution. And that solution then usually gives you adequate number of cells and also has ability to have HPV cotesting done on it.

So, just one swab. Sometimes the canal can be rather dry and a little trouble getting it in. So sometimes I'll just probe with my gloved finger, just gently probe the sphincter to figure out which direction that sphincter and anal canal is oriented to because you can't put lubricant on there. And then I can sometimes get the swab in if it's hard to pass it on the first try.

And then after you do that and collect that, then do your digital anorectal exam. Again, the IAN Society has a great paper on how to do a DARE. And you're feeling the entire circumference of the anal canal, from proximal to the internal sphincter to the distal anal verge. And you can do that either sweeping motions as you're coming out. I like doing it in linear, long motions all the way around. I like to feel the prostate. Some people think that prostate palpation isn't of value, but I have diagnosed a couple of prostate cancers that way during my anoscopy. And then you're done. So just the swab collection and the digital rectal exam at that point in a primary care setting.

Dr. Wood

I think those are really valuable tips.

hpv-anal-testing**[29:03] HPV Anal Testing**

Dr. Wood

On the point about cytology and HPV cotesting, I noticed in the guidelines there are algorithms if HPV cotesting is *not* available. What's your sense about how often HPV cotesting is or is not available with cytology? And any advice for clinicians who may not have access to the HPV cotesting part?

Dr. Schouten

I think it's important to note the FDA has not approved HPV anal testing. It's not FDA-approved. No one's done the quality assurance work to show that there's a concern about interfering with fecal stool and things, that it may not be as accurate as it is in the cervix. So, all these kits are usually in-house assays that are being done, Luminex or other in-house assays. Some will just test HPV high risk, yes or no. Most of them are stratifying. What our pathology department is doing is testing individually for type 16 and type 18; 16 accounts probably 75% of the cervical and anal cancers. That's the one we're most concerned about. Type 18 also, a little more so.

And then there's a group of about 12 other types of high-risk that our institution doesn't test individually but tests in the aggregate. I see a lot of quotes, "other types" come back positive. It's one or more of those other types, 35 and some others, that may not be as higher risk for anal cancer, but we just don't know. So, we have tens of thousands of swabs since we collected them every six months. The reason we haven't run them yet is Joel Palefsky, the PI [Principal Investigator] of this study, is working with the FDA and a couple of testing companies to come up with an agreed-upon platform and plan that when we run them, they then will be submitted and hopefully get FDA support for approval for anal swab testing for HR [high-risk] HPV typing.

And should note you cannot self-collect anal swabs. Occasionally, I've seen some swabs come to our pathology department, self-collected. There's certainly self-collected swabs in the cervix for HPV testing. And HPV testing is more acceptable now and is an option for screening for cervical dysplasia without cytology. In the anal canal, we don't have that. And no one knows what the data is on HPV testing alone. You know, it has to be done in a context with cytology, and you cannot self-collect cytology swabs. Even a provider, as providers saw doing anal cytology, you'll see a fair number of unsatisfactory cytology samples. It takes time and skill to get good samples. And I still occasionally get unsatisfactory samples. So, you have to have that provider collect it though.

Dr. Wood

Got it. That's good to hear. I'll feel less bad when I see unsatisfactory samples.

Dr. Schouten

Well, that's why when you look at the guidelines, they all address: What do you do with that unsatisfactory cytology? And when you look with the cotesting, there are some subtle differences between IANS and the CDC and what we've developed at the Madison Clinic for our guidelines. But everyone is kind of just stratifying, trying to get the highest-risk people for HSIL in now, not everyone.

Dr. Wood

That makes sense. And for listeners, there are tables in the guidelines that you can look at that help to interpret results of the cytology and HPV cotesting if you do it. Again, that's for clinics and centers that have

access to an HRA referral specialist.

standard-anoscopy-tips**[32:14] Standard Anoscopy Tips**

Dr. Wood

Let's turn, Jeff, to the clinics, which are many in the country that do not have access to an HRA referral specialist, at least not yet. So, that is another part of the algorithm in the guidelines. So, for clinicians that don't currently have access to HRA, the guidelines say for any symptoms or abnormalities on DARE, clinicians should do a standard anoscopy in the exam room. But what advice would you give to clinicians who are performing that exam procedure, who are doing DARE and standard anoscopy? And what should they do if they find abnormalities?

Dr. Schouten

Even in people presenting with symptoms such as anal pain or bleeding, most of those are going to be due to fissures, fistulas, hemorrhoids, acutely perirectal abscesses, and perianal abscesses. Most of them are not going to be due to cancer. But if you want to find that uncommon cancer, and diagnosing early is of great value in treatment and outcome treatments for anal cancer, then you need to be referring those people to a general surgeon or a colorectal surgeon for follow-up for evaluation. If you see hemorrhoids, just treat the hemorrhoids, and make sure they have symptoms resolved when they resolve. Same in anal fissure; you can treat with some topical nifedipine or whatever. And obviously if you suspect a fistula, that needs to go for surgical evaluation.

The other thing I would say is at office-based anoscopy, most of these high-risk lesions are the most subtle lesions. One thing you learn very quickly when you're learning how to do an anoscopy, is the most obvious things are probably not the high-grade lesion. Condyloma is much more obvious. And with the combination of acetic acid that we use and iodine, lesions are much more evident. There's a limited amount that you can see with bedside anoscopy without a microscope, without iodine, and without vinegar. But you're going to see gross abnormalities essentially, and those are the ones that probably you would refer on to your general surgeon or colorectal surgeon if you think it needs to be treated.

screening-red-flags**[34:13] Screening Red Flags**

Dr. Wood

So, for clinicians screening for anal cancer doing DARE and anoscopy, what would be the highest concern or the red flags for HSIL and concern for cancer? And as a corollary, what if the clinician encounters rectal warts? What would be the best next step if encountering rectal warts?

Dr. Schouten

Yeah, great question. So, we have a couple of writing committees. And one of the papers we're writing on are the prevalent cancers identified at baseline, and we have about 30 of them that we identified at screening who then were not eligible for the study, obviously. But those would be firmness in duration or a hard mass. If you feel something firm or hard, that's significantly abnormal. That's what you really want to pay attention to. Sometimes you can feel anal papilla at the anal verge, so small polyps that are normal variants on anatomy. You can feel those. Those feel polypoid. You can move them around. I don't worry about those. You generally don't palpate internal hemorrhoids. You'll see them when you put the anoscope in. Generally, they're not palpable unless they're thrombosed. But really, a firm, hard mass. That's really what is most concerning. When I see people referred to me with new anal symptoms and I do the rectal exam, then I know I probably have someone who's got an invasive cancer at that point, even before I put the anoscope in.

rectal-warts**[35:35] Rectal Warts**

Dr. Wood

Jeff, what if the clinician does not see anything like that or feel anything like that but does encounter rectal warts? What I'm wondering is the next step, and in particular, how does a presence of rectal warts...what does that trigger in your mind in terms of risk of HSIL and anal cancer?

Dr. Schouten

There's not that strong an association with rectal warts. In fact, a history of perianal warts in male or females is one of the Risk Category B, the lower risk categories for anal cancer in that IANS paper. There's actually very little data. It's actually in the unknown category of data of anal cancer incidence in people with rectal warts. Rectal warts are obviously due to non-high-risk strains of HPV 6 and 11, the two most common that are in the GARDASIL 9 vaccine.

Oftentimes, I'll see people in their 60s with high-grade dysplasia who had rectal warts when they were in their 20s. That's a more common scenario. Most people who have anogenital warts soon after sexual activity resolve them and clear those non-high-risk strains of HPV. The only challenge, sometimes you can see high-grade dysplasia mixed in with a rectal wart. So, you can see HPV high risk and low risk in the same lesion. Those lesions tend to be Lugol's negative when I do an exam. That always raises my suspicion, whereas a lot of warts are Lugol's positive, so that helps in terms of as an anoscopist. But I will biopsy them if they're atypical if they have atypical vessels. Sometimes, you will see high grade in them. But for the most part, anal warts in and of themselves don't part that much risk for anal cancer other than if they happen to be men who have sex with men or living with HIV.

hpv-vaccinations**[37:11] HPV Vaccinations**

Dr. Wood

You also triggered in my mind just a reminder to emphasize to everyone, remember HPV vaccination as another important part as primary prevention for high-risk HPV and anal cancer. So, another reminder to underscore for listeners.

Dr. Schouten

And it is primary prevention. We've done studies of secondary prevention that are negative. So, there's not much therapeutic value in vaccinating people who already have one of those nine strains. It is permissive to vaccinate up to age 46, with the logic that probably people won't have acquired all nine strains. So, that's why I do vaccinate older people if they're sexually active and going to be exposed to new strains of HPV. But there's no therapeutic benefit for that to acquired strains, unfortunately.

Dr. Wood

I'm glad you added that, Jeff.

future-research-priorities**[37:54] Future Research Priorities**

Dr. Wood

Before we wrap up, this has been incredibly valuable. I think listeners and clinicians will benefit. I certainly have learned from you today. Let me just ask before we close what you see as priorities for future research in this field.

Dr. Schouten

So, in terms of future research fields, we still had a fairly high rate of anal cancer in the [ANCHOR trial] group that was being treated aggressively with office-based ablation, which is hyfrecation electrocautery. A lot of us started out with infrared coagulator but switched to the electric hyfrecation, which is quicker and easier. So, it's simple, but we need better treatments.

As I said, this is a field defect. We're treating localized lesions. Over 50% of people in ANCHOR needed more than one treatment. And one of the risk factors for anal cancer was people with greater than 50% circumference of HSIL at baseline were at increased risk for anal cancer, even in the treatment group. So, we definitely need more treatment options. There are some therapeutic vaccines in development. There's a CMV [cytomegalovirus] vector vaccine that's going into clinical trials soon, designed as a therapeutic vaccine. There's some other topical cidofovirs and a few other approaches the AIDS Malignancy Consortium is looking at, but we definitely need better treatment for HSIL than what we have available, so that's a big issue.

take-home-messages**[39:15] Take-Home Messages**

Dr. Wood

Let's close, Jeff, with what do you see as the most important take-home messages?

Dr. Schouten

I think that the most important take-home messages are think about anal cancer, do the digital anorectal exam on people living with HIV, per the guidelines. And then try and work with your institutions and try to figure out how to build capacity around HRA programs, because they clearly are beneficial and clearly needed, and very challenging to build up and train people. We haven't been as successful as I would like, certainly, over the 14 years I've been doing this.

Dr. Wood

So, incredible progress with results of ANCHOR study with, finally, national guidelines for anal cancer screening, and a lot of work to be done towards implementation and making the guidelines successful.

Dr. Schouten

Thanks, Brian. Been a pleasure.

credits**[40:00] Credits**

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