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Dr. Fuchs: 00:06 Good afternoon, I'm so pleased as we start the fall and, in some respects, the academic year. We have two really exceptional members of our faculty and speakers for today. So our format, as is often the case, today are two topics on pivotal areas of cancer medicine and research that we're going to share with you. And we're going to start first in the area of cancer microbiology. As you know, one of our seven research programs had been virus and other infection-associated cancers, AKA VOIC, but as we sort of realized the increasing impact of things including the microbiome in cancer, radiology, cancer development, cancer progression and cancer therapy, we actually recently renamed that program to cancer microbiology, realizing the full scope. Dr. Fuchs: 01:13 And today's first speaker is really exemplary of the great science we have in this area. Dr. Linda Niccolai is a Professor in the Department of Epidemiology of Microbial Diseases. She is a member of the Cancer Center Prevention and Control Research Program and serves as Co-Director of the Connecticut Emerging Infections Program and Director of the Developmental Core for the Center for Interdisciplinary Research on AIDS. Her research has really spanned the understanding of sexually transmitted infections as it relates to cancer, and I think her pivotal work in HPV, I think, has had important impact both in really biology and actually public health. Dr. Niccolai: 02:07 Thank you. What I'm going to do today in the 20, 25 minutes or so that I have is provide for you the framework that I like to think about as I do the work I do in monitoring impact of vaccines against human papillomavirus, or HPV. I'll spend most of my time talking about our findings and the results to date from this body of research. And then I'll end with a few brief slides about some really exciting future directions, important directions, for this work to keep it all moving forward. Dr. Niccolai: 02:53 So the translational research framework, many of you are probably familiar with this. So this is an image that I like depicting all the different stages. So starting at T0, or basic science research, preclinical, mechanistic animal studies and things like that, through several phases of clinical research and then ultimately hopefully ending up in the world of translation to community impact, population-level impact on reducing the burden of the diseases that we're studying. In other words, a true benefit to the public. Dr. Niccolai: 03:27 So when we think about that for HPV vaccines, I think, arguably, you could say that it all began with the discovery of HPV, the virus that causes cervical cancer. Dr. Niccolai: 03:48 Then moving along, Doug Lowy, who we were fortunate to host here last year, and John Schiller made the discovery, and I would argue this is really T1 research, that the proteins on the outer membrane of the virus can form virus-like particles that can trigger an immune response in humans. And that was really the proof of principle work for vaccine development. Dr. Niccolai: 04:10 So moving along the translational continuum, that work led to the development of vaccine candidates that were tested in phase III, the pivotal phase III, randomized controlled trials. We think of this as T2 research. And these were the findings from those large, randomized trials showing safety and efficacy of the vaccines,

which led to FDA approval. Dr. Niccolai: 04:34 So once we have vaccines, so now we have vaccines that are safe and they're very efficacious in clinical settings. So now we enter the realm of T3 and T4 research, looking at clinical effectiveness and population impact. And this is really where my work has been, and these are the results that I'll share with you all today. Dr. Niccolai: 04:52 So what do I mean when I say clinical effectiveness and impact? Well, this is a really nice article that takes the translational research roadmap and how does that apply to vaccine epidemiology? And it's a little hard to see. It's kind of small, but again, the T2 research, or the efficacy research, is the randomized controlled trials in controlled clinical settings, which we knew from those trials I showed you published in Lancet and in The New England Journal. We know from randomized controlled trials in the controlled setting of clinical research that HPV vaccines are incredible. They're highly efficacious, near perfect efficacy of over 95%, so that's good. Dr. Niccolai: 05:32 But as we enter a practice and community, we don't experience the same controlled settings we do in clinical trials. So here we need to ask questions. As the vaccine is being used in the real world setting, in clinical practice outside of randomized trials, how effective are they? So that's T3 researcher effectiveness. And then ultimately at the population level in communities, important for public health, is what is the overall reduction in disease due to vaccination programs, the way that vaccines are being administered and given, that some proportion of the population does in fact get immunized, what kinds of benefits are we seeing at the population level? So again, T3 and T4 is where my work falls. Dr. Niccolai: 06:18 So quickly, before I get into our work and some of our findings, I'll just want to give a brief overview of the timeline of the HPV vaccination program in the U.S. This is a long story. I've tried to make it short, but just so you know what it is we're trying to monitor the impact of. Dr. Niccolai: 06:34 So the first vaccine in the U.S., the quadrivalent vaccine, was approved in 2006. At that time, there was a recommendation for routine administration to females at ages 11-12, catch-up to age 26. In 2009, a permissive recommendation was added for boys, so they could be immunized, but it was not a routine recommendation. And then in 2011, that did in fact become a routine recommendation for males. So that routine recommendation at 11-12 was harmonized for males and females. But the catch-up age range was a little bit different. Only to 21 for males. In 2015, the 9-valent vaccine was approved. And this is currently the only vaccine that's available in the U.S. In 2016, the dosing regimen changed from three doses to it can now be given in two doses, if started before 15th birthday. And then most recently, just last month, the recommendation changed again. So you may or may not know that they harmonized the catch-up recommendation for males and females. So now men and women should all be immunized up to age 26, and there's now also a shared clinical decision making recommendation up to age 45. So that's where we are. Dr. Niccolai: 07:40 So given these recommendations, how are we doing with coverage in the U.S? I just summarize this as saying we're doing okay, but not great. So this slide shows HPV vaccination coverage in the U.S. since 2006, and you can see that we have achieved about 68% coverage among adolescents with at least one dose of the vaccine initiated this series.

And that only about half of all adolescents have completed the two or three dose regimen. So that's really not great. It falls pretty far below the Healthy People 2020 goals of 80%, and it falls quite a bit short of the other vaccines that share the same recommendation for routine administration to all adolescents at 11-12. You can see those top lines are for Tdap and meningococcal. Dr. Niccolai: 08:29 So that gap between the near 90% coverage for Tdap and meningococcal vaccines down to 50% or 60% for HPV vaccine really represents substantial missed opportunities to immunize a lot of adolescents, leaving many adolescents vulnerable to HPV infections that can cause cancer later in life. So that's kind of a problem. Okay, so now given that that's sort of the landscape in the U.S. in terms of the vaccines we have and the recommendations and the coverage, again my work has really been what is the impact? What is the effectiveness of this level of coverage? So I'm going to talk about three related projects, shown here on the slide. And what I'll do is I'll just give a very brief, one slide each, background on our methods all together and then I'll go into the results. Dr. Niccolai: 09:18 So this body of work really began in 2008 with the implementation of statewide, population-based surveillance here in the state of Connecticut for high-grade precancerous cervical lesions or cervical intraepithelial neoplasia, grades 2 and 3, and adenocarcinoma in situ, which I will refer to as CIN2+ throughout this presentation. Dr. Niccolai: 09:40 So we have had, since 2008, in Connecticut, statewide reporting for these conditions. All pathology labs that serve Connecticut residents are in compliance with this reporting requirement. And they report these diagnoses to us, and we've had over 20,000 cases reported to us since the beginning of this project, and we get limited basic clinical and diagnostic information from the pathology reports. So this is work that we're currently doing with the Connecticut Emerging Infections Program here at Yale, which is a partnership with the Department of Public Health. And the reason why we can do this is because the Department of Public Health, in 2008, added these diagnoses to the list of reportable diseases in Connecticut. So these conditions are required by state statute to be reported to us. We have really complete case ascertainment. So that's our statewide surveillance. Dr. Niccolai: 10:31 So then what we do in our second project is we take that statewide surveillance system and we're doing a project called the HPV-Impact project, which is enhanced surveillance. So I call the statewide basic. This is enhanced. So what we do for residents of New Haven County, who are ages 18 to 39, we collect some additional information beyond what's on the pathology report. And we've initiated enhanced surveillance in Connecticut for over 5,700 women to date. This is work that's funded by the Centers for Disease Control and Prevention, again called HPV-Impact. And we're actually one of five sites across the country doing this. You can see that on the map. So what we do for residents of New Haven County is we collect vaccine histories, and we do that by doing medical record reviews. We've reviewed over 5,600 medical records to date. We do patient interviews when we need to get more information. We've done over 1,000 interviews with these women, and we go to the pathology lab, and we collect residual diagnostic biopsy tissue to send to the CDC for HPV DNA typing. And we've done that for over 3,000 women,

so far. Dr. Niccolai: 11:36 And then our third project, so based on that project, HPV-Impact, the enhanced surveillance in New Haven County, we're doing a case-control study called the "Effectiveness of HPV Vaccine by Age at Immunization as Used in Clinical Practice." So what we do in this project is we take the women from the enhanced surveillance HPV-Impact project who have cervical lesions with HPV 16 or 18 detected. So these are vaccine-preventable lesions, and we enroll them into a study as cases. And then we enroll a group of control women. These are women who have normal Pap smears. So these are women who don't have high-grade lesions by evidence by the fact that they have normal Pap smears. And we do data collection for them to get, we do interviews and medical record reviews to learn about vaccine history so we can compare, in our cases and our controls, women with vaccine-preventable lesions and women without, what do their vaccination patterns look like? Dr. Niccolai: 12:30 So those are the three studies. So now I will talk about our results, and I'll start with our T3 work. So looking at effectiveness in clinical settings. So this is work from our case-control study done by Dr. Carlos Oliveira, who's a Pediatric Infectious Disease physician here, and he did this for his Investigative Medicine Program thesis. And what he found was a significant reduced risk for acquiring an HPV 16/18-associated lesion in women. And what he found, if you look in the red box, so he did a conditional logistic regression using Bayesian model, averaging to control for confounding. And you can see the overall effectiveness. So how effective was having been immunized against getting one of these lesions of 42%. However, if women were immunized before the age of 18, the vaccine was 77% effective. And if immunized 19 or older, it was 28%. So you can see there's greater effectiveness when the vaccine is administered at younger ages. Dr. Niccolai: 13:40 Now that may seem obvious to you because we know these are prophylactic vaccines. They have to be given prior to an infection, through natural exposure, to work. And as women age, their risk of acquiring HPV naturally increases. So clearly, it should be obvious, that it's going to be better when given at younger ages. That's why we recommend at 11-12. The reason why this work is important is because we have a real problem in this country with delayed immunization. A lot of, not only parents, but also providers, are really reluctant to give this vaccine at 11-12. They think their patients aren't at risk. They think their kids are nervous, and they want to push it out. So even though we know in theory it's better when given younger, we can actually show with these numbers, we can now say to clinicians and to parents, "Well, if you do it before 18, 77% effective and if you wait, it becomes only 20% effective." So we felt like having these quantified empirical estimates can be a real potent incentive to both providers and patients and parents for immunizing on time. Dr. Niccolai: 14:48 We've also shown effectiveness by number of doses and this is from the 5-site, the multi-site HPV-Impact project. So again it's a 3 dose regimen at ages 15 and older and a 2 dose regimen of started before the age of 15, but a lot of women in the real world, which is where we're working, this is our space as it's being administered in practice, only get 1 dose, or they get 2 when they should've gotten 3. So what we showed in this analysis was vaccine effectiveness by number of doses. And you can see 47% effectiveness for 1 dose,

55% effectiveness for 2 doses, and greater than 70% effectiveness for 3 doses. Dr. Niccolai: 15:28 So what we take away from this is that even 1 dose provides a good amount of protection, but 2 and 3 doses are even better. So we really should, in this country we have a 2 or 3 dose regimen, and we really should be sticking to that. And you can see how effectiveness falls off. And again, this is why this post-licensure, real-world effectiveness work is important. We know from the randomized trials, efficacy is 95% or greater. And when we look and see how fall short of that do we fall, we can identify opportunities for improvement. So here you can see that really what's the reduction in benefit at getting 1 dose or 2 doses, when we really should be giving 3 doses. So important to quantify these gaps so that they can be addressed. To what extent are we achieving the full prevention potential of these vaccines? Dr. Niccolai: 16:20 And we've also looked at trends in HPV 16 associated cervical pre-cancers by vaccination status. So looking at women who have pre-cancers, we looked at the women who their precancerous lesions had HPV type 16 or 18, the vaccine preventable types. And we can see over time a significant and substantial reduction in vaccinated women. So over time, women who were vaccinated, the proportion of those lesions that were vaccine-preventable has come way down from 55% to 33%, and we really haven't seen a similar thing among unvaccinated women. So this is our T3 work, this is effectiveness. How effective are the vaccines as they're being used in real world clinical practice? And I think we've shown pretty good impact, falling short of the randomized trials, which we would expect, but pretty good impact so far. So this is really good news for vaccinated women. Dr. Niccolai: 17:12 But what about the entire population? If the entire population is of interest to you, we really want to know how are these vaccines driving down the burden of disease? So these are data from our statewide surveillance project in Connecticut showing trends in cervical pre-cancers by individual age in years over time from 2008 through 2017, and what you can see are some really nice declines. So for example, if you look at the red line, those are women age 21. Since 2008, their rate of precancerous lesions has declined by 75% and in the blue line, women age 22 is 71% decline. In the green line, women age 23, a 60% decline, and so on. So this pattern of earlier and larger, progressively larger, declines by age, by individual years of age, is really consistent with, it's exactly what we would expect from vaccine impact. And the declines are pretty substantial. And these are residents of Connecticut, so very local. Dr. Niccolai: 18:23 We've also shown, and these are data from the 5-sites study, showing declines in women adjusted for screenings. So arguably on the previous slide, some of those declines could be due to changes in screening. If we're screening less frequently, maybe we're detecting fewer lesions. This slide shows the declines when we account for screening in the population and you can still see declines. 39% decline in women aged 18 to 20 and a 36% decline in women age 21 to 24. So population-level impact, again, this does not account for vaccination status. This is just in the entire population. How are we seeing the burden of disease come down in this era of vaccination? Dr. Niccolai: 19:05 So this is a slide also from the 5-site project showing what they did. In this analysis was they took the rates of CIN2+ that we observed in our catchment areas and

projected that to the entire U.S. population. So if you look at the bars kind of on the left, you can see that in women age 20 to 24 in 2008, so prior to vaccine impact, there were nearly 60,000 cases of CIN2 diagnosed every year. Today that number is fewer than 20,000, so population-impact. Dr. Niccolai: 19:40 And finally the last results slide I'm going to show is this is data from the HPV-Impact only in Connecticut where we looked at trends in pre-cancers, again that detected with 16/18, so vaccine-preventable lesions, and we looked at this by area-based measures of race, ethnicity and poverty. So we're starting to think a little bit about disparities here, and I'll just walk you through the blue bars for poverty. But there's a very similar pattern for race and ethnicity. Dr. Niccolai: 20:10 So you can see in the three blue bars on the left, so these are areas of high poverty, so communities where a lot of women are living in poverty. You can see the proportion of lesions with 16/18 detected. Again, the vaccine-preventable lesions, it kind of bounces around a little bit. It's not entirely clear what's happening. But if you look in areas of low poverty, where fewer than 20% of the residents are living in poverty, you can see this really nice decline in vaccine-preventable lesions. So that kind of makes sense. We're not quite sure what to make sense of the women living in the high poverty areas, but at a minimum, this suggests we really need to do ongoing continued and vigilant monitoring of health disparities. Dr. Niccolai: 20:54 So those are just some highlights. We've done a lot more work with these data that I'm happy to share. But I think the take home message here is that vaccines are really having impact, right? No matter how we look at it, when we look at it, where we look at it, or what we look at, every time we've looked at anything related to impact, we're seeing impact. So that's good news. But then I always like to remind myself and others that that's good news that could be better. We've achieved this with moderate coverage, so that's exciting, but what could we be achieving with higher coverage so we can just keep driving down the burden of disease in communities? If we could get that coverage up from 50-60%, remember I showed on that earlier slide, up to 80 or 90%, which is entirely achievable in the U.S. Dr. Niccolai: 21:43 So five more minutes and I'm just going to talk a little bit about some future directions that I'm personally very excited about. I know other people in the room are too. So this is great work. We've been doing this for over 10 years. We'll continue to do this. There's lots more work to be done, but we've been looking at precancerous lesions. So now what about cancer? What about invasive, cervical carcinoma? And maybe we need to be doing more with health disparities as well. Dr. Niccolai: 22:10 So this slide is probably very familiar to you. Declines in cervical cancer. We've seen over time huge public health success story and in large part attributed to screening and treatment. So this is great. But if you look a little bit closer, you might see a leveling in the rate of decline. And in fact, I've put up here the incidents rate estimates for 1975, '85, '95, 2005 and 2015, and you could really see not much progress over the past decade. So it's possible, you could speculate, that we have achieved what we can achieve with screening, that screening has driven this way down, but now we're kind of stuck at 6 to 7 new cases per 100,000 women. So here we are, right around the same time that this was plateauing, HPV vaccines

were introduced. Dr. Niccolai: 23:02 So this really begs the question of "What is possible now?" And people are really saying cervical cancer elimination. I mean think about that. Elimination of a cancer is now possible. In 2018, the Director-General of the World Health Organization, you can read his quote here, called for efforts to make cervical cancer history. This was joined by numerous organizations, and this is really all the buzz now in the research communities and probably in clinical communities and in public health communities, that cervical cancer elimination is now possible. Dr. Niccolai: 23:40 And modeling studies show it could happen within many of our lifetimes. So this is a figure from a modeling study in Australia. And just focusing on the red line showing the projected incidents of cervical cancer going forward, you can see that by 2020, that's next year, they expect to achieve 6 new cases per 100,000, which is the definition of a rare cancer. By 2028, a decade from now, they expect to be at 4 new cases per 100,000, which is the threshold that's been set for elimination. That's the elimination threshold. And then it just goes down to practically zero. So this can happen and it can happen soon. Dr. Niccolai: 24:19 The question is whether or not we're going to make equitable progress toward this goal. This we really don't know. There are disparities in cervical cancer incidents and mortality in the U.S. The disparities have diminished with screening, but they have persisted. There are higher incidents rates in Hispanic women and higher mortality rates in black women. And what we don't know is if these disparities will disappear or grow with the HPV vaccination program we have and how that's being sub-optimally used in clinical practice. Dr. Niccolai: 24:54 So we've been working on a grant proposal. This is a due in October, so coming right up. It is a P20 application, I believe. So it's a developmental SPORE, Specialized Program of Research Excellence, focused on cancer disparities. So it's not a particular cancer or a site. It's cancer disparities in general. It's being put in by Melinda Irwin and Andrea Silber, and we are doing one of the research projects for this SPORE application. So we've come up with an idea to look at cervical cancer and health disparities in this era of elimination, and we'd like to use an interdisciplinary approach to identify multi-level risk factors. So here are 3 specific aims. Basically we want to look at trends in cervical cancer in this era of elimination by race, ethnicity, and income. We want to look at risk factors. So we would do that using a surveillance approach very similar to our statewide surveillance, and then do a case-control study, like we're doing for pre-cancers, do the same thing for cancer and look for risk factors related to race, ethnicity, and income. Dr. Niccolai: 25:56 The question really is: in this era, cervical cancer is preventable with the tools we have between vaccination screening and treatment. It really should be prevented. So the question is: in this era of prevention, who continues, which women and why are women continuing to be diagnosed with cervical cancer? We'll try to answer the why question with Aim 3, really looking at social and structural barriers to prevention and in paying particular attention to factors related to race, ethnicity, and income. Dr. Niccolai: 26:27 So here's an overview of the study design. I won't go through this, but I will say that again, this is a grant proposal in progress. So if you all have thoughts or suggestions or questions or comments or want to collaborate,

please do let us know. It is going to be interdisciplinary in terms of using surveillance approaches and molecular epidemiology, risk-factor epidemiology, and qualitative research. So we really hope to get a complete picture of what's going on with cancer in the coming years. Dr. Niccolai: 26:59 So I did it in 25 minutes. I told you I would. So in conclusion, again, good news that could be better. I think many of us working in this field are surprised by the impact these vaccines are having. I think the magnitude of the declines with something that really has surprised us all a little bit, but maybe if you think about the fact that even though our coverage is suboptimal, when you have a vaccine that's 95,97% efficacious, getting that out in the population can really make a difference. Dr. Niccolai: 27:27 So while it's encouraging that moderate vaccine uptake can be impactful, I think the glass can be half full or half empty. I think the other half of that story is that this is really, we should be doing better with coverage and that's a whole nother area in which I work. Topic for another day. And really here we are in 2018, 2019 starting to think about eliminating an important cancer. So very exciting. Many, many, many, many thanks, folks who are here in the room, to all of the people who made this possible. Too many people to name, some of them are named on the slide. I really want to thank all of them from the bottom of my heart for their effort and commitment to this important area. It would not have been possible without them. And thank you all for your attention.