We have Dr. Kevin Winthrop joining us today. Kevin is a fantastic speaker. He is an expert in this field. And I'm sure he's going to enlighten us on the latest information on the best ways to diagnose, as well as potentially treat, patients who are going to get this biologic agents and the best way to prevent the disease. Kevin is an Assistant Professor of Infectious Diseases and Ophthalmology in Public Health and Preventive Medicine at the Oregon Health and Science University. He's also a former staff for the Infectious Disease Epidemiology Division of the CDC with the TB elimination.

Kevin, we won't hold that against you.

He has co-authored over 130 publications. He is a leading researcher in the field of TB and NTM, especially in studies dealing with biologics. Today, he's going to be speaking about TB and biologic therapies, their risk and prevention.

Kevin, without further ado, all the way from Oregon, we're just so happy to have you. Kevin, how's it going out there?

Good, Dave. Thanks very much. Can you hear me okay?

We can hear you great, Kevin.

Perfect. Well thanks, everyone, for joining.

And, Dave, thanks for inviting me to give this talk. It's a talk I like to give, and these are the areas that I'm really active in, in terms of research and what I spend my time thinking about outside of normal life.

I apologize, too for being a few minutes late here. I was in clinic, and of course the last patient showed up with an O2 sat of about 84 or 85 at 9:30 a.m. my time. So it was a quick turnaround to try to get here on time; so thanks for bearing with me, everyone.

That being said, I think I probably have 45-50 minutes of material to talk about; and I'm definitely happy to discuss things in more detail by question. Why don't we launch ahead into the talk? I think I have controls here.

Those are my disclosures. Almost all of this is drug safety work, either on data safety monitoring boards or looking at clinical trial data trying to look for safety signals. That being said, let's talk about TB.

You all are TB people -- or most of you probably on this call -- and you know this map. This is really a map probably for non-TB people to look at. But just as a reminder to start the talk, you know where the areas of endemic TB are. I think to set the stage for this talk, most of these areas have not been areas where the drugs I'm going to talk about today have been used. The clinical trial development programs of many of these drugs have enrolled patients from some of these areas; hence, we know about TB risk with some of these compounds because of that.

But in terms of widespread circulation and post-marketing use, most of these drugs have been used in the Western Hemisphere: North America and Western Europe. This is now changing, really in the last year or two, where generic forms or biosimilar forms of these drugs are being manufactured. And we're seeing more use in India and China and places like that, where there's much higher background levels of TB. So this is an ever-changing situation, and I expect to see more and more TB worldwide as these drugs become more widely used.

TB pathogenesis, just to review – again, you know this. Most of TB is transmitted through inhalation. And once the TB bacilli is inhaled, the alveolar macrophage picks it up. Within the macrophage of course, TB,

the bacilli, wants to be there. It replicates, and it eventually bursts out of the cell and spills and disseminates hematogenously.

At this point, the body attempts to react with really multiple forms of immune defense. Most of this is based on TNF-alpha responses and interferon-gamma responses. These are Th1 immune responses. And most of this hinges on your system or the immune system limiting the spread of infection by granuloma formation around the bacilli and intracellular killing of the bacilli. Again, these processes are closely linked to TNF-alpha and interferon-gamma. These important cytokines can be, as you'll see, will be down-regulated, or inhibited in some cases, by some of the therapies I'm talking about. That forms the basis of our understanding of the risk of some of these compounds. I'll go into this in more detail.

The main goal for this talk is right here. I am hopeful by the end of the talk that you will have learned how to pronounce at least one of these drugs' names. I've spent months, and sometimes years, trying to get the pronunciations right. It's not easy. And of course these aren't the trade names; these are the generic names, but the trade names aren't much easier in some cases. The TNF blockers we have up above and the ones in gold are the ones that have been around the longest -- really 8-plus years, 10-plus years for infliximab and etanercept. Adalimumab was a few years later, I think 2006; it was approved around that time.

The bottom line is most of what we know about TNF blockers comes from long-term safety data, experience, observational studies with those three drugs. We know relatively little about golimumab and certolizumab because they're much newer to market. They get lumped in with the other monoclonal antibodies, like infliximab and adalimumab; and we assume their safety profile is similar, but we really are just making an assumption. The etanercept is slightly different. It knocks out TNF, but it's a p75 receptor that floats around rather than a targeted monoclonal antibody that zeroes in on TNF.

Then we have the other drugs: abatacept, which is CD4 T cell responses; rituximab, which depletes peripheral B cells; tocilizumab, which is a blocker to the IL-6 receptor, so it down-regulates IL-6 responses; and then ustekinumab, which is widely used in dermatology now for psoriasis, which blocks IL12 and IL23. And actually, it blocks the P40 subunit that's in both IL12 and IL23; so hence, it down-regulates that. It accesses the immune system, and I'll get into these things in more detail.

Tofacitinib is not technically a biologic; it's actually a synthetic disease-modifying antirheumatic drug or DMARD. It is not biologic because it's not a manufactured antibody or something like that; but it's a drug that inhibits what's called the JAK inhibitor, and I'll go into the JAK system later. I didn't know jack about JAK, I like to say, until a couple of years ago; but I've become very interested in this pathway, and you'll see why in a little bit.

Next slide.

This schematic is just meant to bewilder you, and you don't really have to look at it. I'm colorblind, so it doesn't mean a whole lot to me. But suffice it to say, this is a T cell and a B cell; and there are all these receptor complexes on them. A variety of these drugs target some of these receptors. You can see on the left-hand side there, rituximab is the B cell deplete; it targets CD20, and it will annihilate these B cells. Atacicept/belimumab, these are the things that inhibit things called BAFF, which activate B cells; so they stop activation of B cells. Then you've got abatacept, which basically minimizes the ability of other cells to activate T cells. So if a pathogen is presented or your immune system is trying to react to something, the CD4 T cell takes a variety of signals to get it going. Abatacept interferes with that process.

Dave, can I ask a question? Can you see my cursor, or is that not showing?

I'm not able to see that, Kevin. I think at the top, where you see the arrow where it says Draw -- right. Now I can see you, Kevin. Great work.

There you go. There's abatacept right there; and it interferes with this step where this ligand on the T cell is ligating itself to this ligand on the B cell, and this is what activates the CD4 T cell. But Abatacept gets right in between there and prohibits that from happening. Great.

Next.

Before I get wild and talk about all these drugs with weird names, let's talk about prednisone. This is my soapbox part of my talk. There's really no question that prednisone increases risk of a variety of infections, including tuberculosis. This was talked about in CDC's LTBI statement and prior TB statements for years, but there was really never any data, ever, cited that was worth a darn to substantiate that until this publication in the rheumatology literature in 2006. This was a general practice research database study, where they took all the TB cases in England for a 10-year period; matched them to controls; and found that current glucocorticoid use, or prednisone use, raised the risk of TB about fivefold. There was a dose-dependent risk with higher risk at higher doses. You can see 15 milligrams here; you had an odds ratio of 7.7.

This was really the first study that I could find in literature that really solidly drew the line here. Since then, there have been other studies; but there's no question that prednisone is a bad actor. One of the benefits of the biologic drugs -- and I'm not going to go into this specifically, so I'll say it here -- is that if you can start a biologic drug and get someone's underlying rheumatic disease in better control, for example, you can decrease or even take away the prednisone. And if you do that, you are benefiting the patient. One reason these drugs, the biologics, look potentially less risky is that they can serve as prednisone-sparing agents. So I am much more concerned when someone starts a biologic but maintains their prednisone dose. That puts you at higher risk than if you are able to wean the prednisone down or off.

Here's a classic x-ray; you are all familiar with this. I show this to my rheumatology audiences all the time; but again, point out the classic sphering, right upper lobe, infiltrating and cavity here. There's also a cavity probably in the right middle lobe there. This is something I use to point out that at least half the patients -- generally speaking, you develop TB in this setting -- have normal chest x-rays. Half this disease is extrapulmonary on average. So many of these patients will not have an abnormal chest x-ray or pulmonary disease.

What is the risk of TB? This is the risk of TB with TNF drugs. There are several studies now that have really firmly established this. They are in areas of low TB incidence. This is the UK study, the French study, and the U.S. study.

In the first row is the UK study. What we see is -- this is the British Biologics Registry. They have all these people that have started TNF blockers; and again, it's etanercept, infliximab, and adalimumab. Then we have people who also have rheumatoid arthritis but are on comparative drugs, such as methotrexate. You can see that the incidence of TB in people on anti-TNF drugs together was 95 per 100,000 compared to zero in the comparative group. There you go -- so 95 per 100,000 versus zero. We know the risk is elevated.

In France, they did a similar study. They found the rate was 117 per 100,000. They did not have a background rate calculated for that study, but that's certainly elevated over the population base incidence, which was around 12 or 15 per 100,000 at that time, if I recall.

In the U.S. -- we actually did this study -- we found the rate to be 56 per 100,000. This was compared to 9 per 100,000 in similar patients, who are not on anti-TNF drugs. When you look at the individual drugs, we found what we now understand to be well-known phenomenon. It's that the monoclonal antibodies were more likely to cause TB than etanercept so I point this out in that etanercept certainly increases risk of TB. The risk was 39 per 100,000. That is above the background rate of England, which was about 12 per

100,000 at that time. I also point out that infliximab and adalimumab were another three- or fourfold riskier in terms of the incidence rate of TB associated with those drugs.

We found a similar finding in our experience in the U.S., so I was happy to see these things. We found roughly half the rate -- which was probably right, given our rate was roughly half of what it is in England. We found, again, a three- or fourfold increase in patients on infliximab versus those on etanercept. You can see again here, if I can figure how to do the arrows, 83-91 per 100,000 for the monoclonals versus 17 per 100,000 for etanercept.

This is a little more information about that study. This study was done in the Kaiser Permanente Northern California database. You can see that we also looked at non-TB mycobacterium, so this is my chance to plug non-TB mycobacterium. This is part of the mycobacterium family. It's my opinion that we should be mycobacterium people; we shouldn't just be TB people or NTM people. We do lots of NTM work in our daily TB jobs in terms of ruling out NTM in the lab and in people, and often treating people with NTM until we find out whether or not they have TB. NTM is a bigger deal in this setting in the U.S.; but again, as a mycobacterial person, I can show you that in the general Kaiser population that NTM was more prevalent. It was about twofold more prevalent, and those rates are about 5 per 100,000 versus a TB rate with 2.5 per 100,000.

Once you look at older individuals, this disparity grows; and the rates grow. When you look at RA patients not using TNF drugs, the rates were, again, double NTM, about 20 per 100,000 versus about 10 in the TB group. And when you looked at the RA patients, this was the rheumatoid arthritis patients on TNF blockers, you see the rate -- about 100 per 100,000 for NTM and about 50 for TB. The rate certainly increases for all mycobacterium in this population with TNF use.

The question has been asked, and there have been a variety of studies that looked at this: Why do infliximab and adalimumab cause more TB than etanercept? There are lots of theories about this. I kind of drew a line through a lot of these theories because I think the bottom two are really the ones that explain the difference; and that has to do with that these drugs can down-regulate interferon-gamma differentially, and they can also penetrate granulomas differentially. I'll show you some of that data.

This was some of the earliest data. This was in vitro data where TB culture filtrate in vitro was looked at using blood of patients on etanercept, adalimumab, and infliximab; and you can see that the stimulated responses of T cells was more diminished in the patients on adalimumab and infliximab. This is the amount of interferon-gamma that was produced in the presence of TB. And you can see a much greater down-regulation for the monoclonals as compared to down-regulation, but a more modest down-regulation with etanercept. Interferon-gamma is, of course, important in controlling TB; and so, again, this might explain why there's a difference between these drugs.

The other study that I'd like to talk about is the Plessner study. These were mice who had up here, they had acquired new infection of inhalation of TB. In A and B up above, these were mice that were – sorry, let's get back to where I'm going here. These were mice that were given a new infection of TB. You can see this is a survival curve. As you go along here, no matter if they were on etanercept or infliximab, everybody died at about 21 days after infection. This was the bacterial burden in the lungs. You can see it rose no matter what drug the mouse was on.

This model, however, in C and D, this is different. This is the latent infection model. These are mice that have chronic latent TB infection; and when you give them these drugs, something different happens. The ones on infliximab all died very quickly; the ones on etanercept, about 60% survived. Again, you see a difference in bacterial burden. It's much higher in the infliximab-treated mice, lower in the etanercept-treated mice -- in the control mice.

When they did autopsies on these mice, what they found was -- you can just read the bottom line here -- that the lung pathology differed. The etanercept penetrated those granulomas to a much lesser extent than the monoclonal. This may be another clue as to why there is a difference here. Perhaps infliximab just penetrates the granuloma better and interrupts cell/cell signaling to a greater extent than etanercept does.

Next.

Here's another piece of data that also might explain why the monoclonals do a better job of causing TB. This has to do with CD8 cells. It's been shown that these CD8 cells directly produce what's called perforin and granulysin. And these two things -- this is perforin on the left, granulysin on the right -- you can see that before modulation with infliximab, the levels are here; with modulation, they go down. You see this decrease in these cells that produce these products, perforin and granulysin, which are directly antimycobacterial cidal. They will kill TB; and this is, again, part of our defense system against TB.

These are probably modulated to a much greater extent with infliximab than etanercept. The authors didn't study that necessarily, but we know that it's membrane-bound TNF that is important in these responses. And infliximab tends to inhibit membrane-bound TNF much more than etanercept. In fact, etanercept doesn't. So this is another potential explanation.

Next.

I've spent some time talking about that, but I want to drive home the point that it's really almost a moot point; all these drugs cause TB. Etanercept increases the risk of TB, but I do believe it does so to a lesser degree than at least infliximab and adalimumab. The other two monoclonals which I mentioned, golimumab and certolizumab, we just don't know; they get lumped in here. But the bottom line is everyone needs to be screened before they start these drugs, and everyone should maintain vigilance for TB during therapy with any of these drugs.

I share this slide; this was a slide that Monty Pye [ph] helped me put together years ago. It's completely out-of-date, but I guess I decided it wasn't worth updating. I just show it because the same heterogeneity and recommendations exist today as it did several years ago when I put this slide together.

You can see here on the left that these are different agencies or countries that have issued guidelines, and you can see what year they were. Some of them are quite old; some of them are newer. We also then wanted to just show that there are differences in opinions here. The original BTS guidelines recommended really no initial screening, but just treat people from highly-prevalent regions with empiric INH. They were worried about false positive skin tests in people with BCG. They were also worried about false negative skin tests in patients who were anergic and immunosuppressed.

Other groups have moved to recommending the IGRA, primarily due to the concern of false positive skin tests. Some people have a two-step procedure with skin tests; and actually, the Spanish still do this to my knowledge. They use a two-step skin test, despite the historic use of BCG in their population. There are a variety of other nuances here, but the bottom line is there's heterogeneity; and that's the point of this slide. Probably the best way to screen probably depends on where you are in the world. It depends on two factors, your regional use of BCG and your background TB prevalence. I'll get more into this in a second.

Let's talk about the IGRAs. There are two IGRAs to choose from, the T-SPOT TB test and the QuantiFERON In-Tube. These are both good tests in my mind. They're very similar in their qualities and in what they attempt to do. Clinically, I tend not to distinguish between them because I think they accomplish largely the same thing. You're all familiar with how IGRAs work, so I won't go into them. But of course they were designed to be much more specific by primarily not turning positive due to BCG. The

antigens, of course, contained in those test have a much higher specificity for TB than PPD does, and so therefore you do not see this false positivity due to BCG.

One question has to do with sensitivity. And really, when you're screening immunosuppressed patients, to me the name of the game is sensitivity. I'm willing to err on the side of a few false positives if I pick up more true positives. And this is how we have approached our life as TB people for a long time now in terms of screening immunosuppressed or higher-risk populations.

This to me was the most elegant look at this issue. This is a case-control study in Peru, where there was heavy BCG use in both groups. And there are two groups of people studied -- the rheumatoid arthritis group, about 100, and about 100 controls. I will point out that in the RA group, there's quite a bit of prednisone use; whereas in the control group, of course, there's no prednisone use. What this study suggested was that the QuantiFERON was more sensitive than the skin test. What drives that conclusion is the fact that in the control groups, about 60% of people reacted positive to either the skin test or the QuantiFERON. That is consistent with other studies in Peru suggesting 50% or 60% of people there do have positive skin tests.

In the RA group however, the rates or the proportions of positives were much lower -- only 27% with the skin test and 45% with the QuantiFERON -- so much higher in the QuantiFERON compared to the TST. The QuantiFERON was a bit closer to the controls; and this difference, between 27% and 45%, was fairly large. The idea was that the QuantiFERON was picking up more true positives here and was more sensitive.

I can tell you without spending an hour going through all the studies in this setting that there's no question prednisone causes false negative skin tests and prednisone also causes false negative IGRAs. But my sense is that the IGRAs hold up slightly better under the conditions of prednisone use as compared to the TST. I do think probably IGRAs are slightly more sensitive in this setting. That's a hard thing to prove because we have no gold standard for LTBI; but if you look at all the data, again, that would be my summary.

Let's talk about more how to screen. And the way I recommend screening is a result of several studies, which I'm about to describe; and it also really takes into account a prior probability. If the patient has risk, you need to screen to a different degree or a better degree than if the patient doesn't have risk. Let's talk about this more specifically.

This is the Kleinert study from Germany. Most of the people in this study had no BCG history. And what really bothered me about this study was the following. They took 1,529 rheumatology patients prior to TNF start or biologic start. Actually, I think it was all TNF blockers. But prior to start, they screened them with both a skin test and an IGRA. You can see, 11% had a positive skin test; and about 8% had a positive IGRA. However, there was very little overlap between the two groups; so very few people were positive on both.

When you looked at people that were positive on the skin test but negative on the IGRA, which is this group in the Venn diagram here, the problem is that a lot of these people lacked BCG; and a lot of them had really big skin tests, like over 15 millimeters. Yet, they were negative on their IGRA. It's really hard to blow this off. I mean, if someone has 15 millimeter skin test; they have no history of BCG; they have no reason to have a false positive skin test; yet they have a negative IGRA. I don't know what that means other than I would be worried about putting that person on a TNF blocker. These are really, to me, positive people; but they're discordant. They're positive on the skin test, negative on the IGRA. So what do you do with these people? I think you have to call them positive.

Next.

In France, basically the same thing happened. And I love this French study because what they did was they took almost 400 people. They screened them with all three; they used a skin test, a T-SPOT, and a QuantiFERON. Most of these people had had a history of BCG. These were the disease groups: AS is ankylosing spondylitis, rheumatoid arthritis, and inflammatory bowel disease. I'll tell you that the T-SPOT and the QuantiFERON concorded fairly well; there was a pretty good level of agreement between the two, which is generally true of most of these studies.

And then in terms of the skin test, there was this group of people that had a greater-than-10 millimeter skin test. So they really were "positive," but, again, most had BCG history. Most of these people were negative, but they were negative on both IGRAs; they weren't negative on just one, but negative on both. If you look at that group, almost all of them were given – that TNFi or TNF inhibition or inhibitors or TNF blockers. Most of these were given TNF drugs without INH, and none of them developed TB.

So I think there was something special about this, in that they used all three. And if you've got a positive skin test but you're negative on both QuantiFERON and T-SPOT, that's probably more reassuring than just being negative on one. Again, these people are distinct from the German study I just discussed. These people had a reason for potentially having a false positive skin test because they had BCG.

Next study and this is the best study. This is the golimumab experience. They screened over 2,000 patients in the development program for golimumab: RA, psoriatic arthritis, ankylosing spondylitis. They screened them with both a skin test and the QuantiFERON in-tube. Five people developed active TB; all of them had screened negative at baseline. But actually, when you looked at that data, two of them were prior positive on their skin test. They were negative on quanti, but positive on the skin test. One had a 5 millimeter, and one at 15 millimeter. But they were judged negative by local standards because these were thought to be BCG-associated reactions.

Really, when you look back, two out of those five probably should have been picked up as positive; and they were picked up by the skin test. Of the 317 people who screened positive, however, I thought this was great. They put them on INH, and they put them on golimumab simultaneously; and they were all treated with nine months of INH, and nobody developed TB. That's important.

But when you look back at the screening results, this is also important; and this is problematic. Again, similar to the German study I showed you, there's very little overlap between people who tested positive to one versus positive to the other. So this group here, this is the BCG group up here. You see very little overlap. You see all these people that are TST positive, this group that's QuantiFERON positive; but very few that are positive on both.

And if you ignore the lower half of this figure and just had the top half, you would say, "Oh, well, this makes sense. These people all had BGC. So this group here or most of these or all of them are probably false positive skin tests." The problem is when you look at the people who lack BCG, and that's the lower group here. When you look at this group, you see the same phenomenon. You see very few people who were positive on both, and you see this big group of people that were TST positive but were QuantiFERON negative. And you can't blame it on BCG because they didn't have it. In fact, when you look at that TST group again, a good proportion of these patients had reasonably sized TSTs, meaning greater than 10 millimeters.

So this is problematic to me, and this tells me that neither one of these tests on their own probably pick up everyone at risk. It leads me to the following screening recommendation. And I've published this; this is my recommendation. It's not necessarily the way to do it; it hasn't been studied for cost-effectiveness and things like that. But it, I think, really just more illustrates how I think about screening.

The most important thing in the world for this sort of thing is risk factors. What is the A-priori probability? If someone lacks risk factors, you really probably don't need to screen them; but they're going on these

drugs, so you should screen them. But I don't try very hard to screen these people; meaning, I don't think they should be positive. I do think about their level of immunosuppression. If they're not very immunosuppressed, then I would just use an IGRA. If they are heavily immunosuppressed, you might just be fine using one of these tests as well; but I talk about a dual skin test approach here.

Let me give you some real patients here. This is my patient from Switzerland; and she was a woman who came to me, and she was in her 50s. She'd had BCG in the past, and she had no risk factors. She'd been in Switzerland her whole life, and now she was in Oregon -- two places where there's virtually no TB. The chance that she's been exposed to TB is almost nil. The fact was that she had already had a skin test, and it was positive.

I saw her, and I did an IGRA; and it was negative. I decided given the fact that she had no risk factors, she wasn't very immunosuppressed either because she hadn't started any of her therapies yet. I thought I could get away with an IGRA alone, and so I deemed her negative. Also, like all good Swiss people, she had a vaccine card in her wallet from 40 years ago, showing me exactly when she'd been vaccinated and with what -- every vaccine, including BCG. So I was relatively reassured that that was her history; and I blamed her 5 millimeter skin test on her BCG, and I felt comfortable doing that. That's this side of the paradigm or algorithm.

Now, if you go to this side with the positive -- so someone who should be positive -- and this is my patient from the Philippines. He was in his 30s; he was an Intel engineer. He's from the Philippines, a place where it's probably a coin flip whether you're infected or not. He was on 60 milligrams of prednisone a day -- so now we're here at this box -- heavily immunosuppressed. His ophthalmologist wanted to put him on infliximab, so I was to screen him. I screened him with a skin test; it was negative. I screened him with an IGRA; it was negative. So he got a dual screening. And then there's a little footnote here that was very CDC-like, I thought; I like this whole recommendation. If you go down to the fine print, it says, "For patients with risk factors and who are immunosuppressed in whom false negative results are more likely, consider repeating a screening test with one or both tools."

I like this advice. So I followed my own advice, and I started back up here, and I re-screened him. And I screened him with both again, and he was negative on both again. So now here's a guy who it's probably 50% chance he's infected, given he's from the Philippines; but he's on 60 milligrams of prednisone, and he's been negative to both tools twice. So I told him what I thought his risks were, and I gave him all his probabilities and statistics; and he was an engineer. We talked about INH and how there was a risk of hepatitis toxicity, but it's minimal in someone his age. We went through everything, and he decided in the end he wanted to take the INH. He, in fact, calculated everything himself. He had a calculator and he was an engineer. He told me he thought it was in his best interest to take INH; I said, "Great." Three months later, he'd weaned off his prednisone; and he was on infliximab. I repeated his screen test, and he was positive. That was with IGRA.

This is an end of one experience. You can't live your life this way, but it illustrates how I think about this. This is a guy who should be positive; he's really immunosuppressed. I just don't know that I can trust his test. And so this is someone I would probably screen more closely or "more aggressively" by repeating tests and using a dual test methodology; as compared to someone on this side of the paradigm, someone in Portland, Oregon, necessarily who has no TB risk factors. I think just using one of these tests -- and I would probably choose an IGRA because I do think it's slightly more sensitive in people who are immunosuppressed. I would screen with one test, and I would not repeat the screening.

I hope that makes sense, but that's how I think about this. In fact, the American College of Rheumatology thinks about it similarly, probably because I was the consultant on these recommendations. But they recommend prior to biologics, start something similar. They say use a skin test or an IGRA. But think about repeating or rescreening if they have TB risk factors and they're immunosuppressed – and, again, largely the same algorithm.

What about serial screening? I'm asked this question all the time in endemic areas. Patients are at risk for new exposure, and so there is an idea that maybe you should screen these people every three months or every six months or every year or something like that. There's really very little data out there to guide us how to do this. There's one study from Taiwan, as illustrated here. They did do this every three months; and they did pick up four or five cases of TB who their QuantiFERON responses -- I think they used QuantiFERON in this. I think it might have been gold, in fact, not in-tube; but they did find an increase in interferon-gamma production, and it coincided with their diagnosis of TB.

My only problem with this study is that they basically did these tests when the patients were starting to feel sick already from TB, which was right here in the time course. It's not like they did them back here and they predicted that they are going to get TB and they prevented it. But it just more, you know, kind of helped them diagnose it at the time. So I'm still perplexed. I'm not quite sure at what frequency we should be screening someone in a highly-endemic area; but I think it's a reasonable idea, and I think it needs further study.

LTBI treatment, you guys know all this. There's one study from Spain in the second bullet there that has showed that if you screen people, start INH, and start their TNF blocker one month later, you can reduce TB rates. And they showed an 83% reduction in TB rates associated with infliximab. There are really no other studies, I think, that are population-based that show just kind of this before and after type of experience. This is the one study that shows it, and I think it's intuitive that we all think that rates have declined since screening has become widespread. LFT testing, just take note, a lot of these patients are on methotrexate; so you've got to be aware of it.

The new therapy option, the 3IR -- this has not been studied necessarily in this setting. It's been studied in the non-immunosuppressed setting, and that's the data presented here from the Sterling paper in the *New England Journal*. This is of course a CDC study of three months, once-weekly INH and rifapentine directly observed, as compared to nine months of INH. And you can see, the TB rates in the two arms were different. They were actually statistically similar; but about half in the combination therapy, so INH/rifapentine, the rate was 0.07; and the rate was about double that in the isoniazid arm. So we know this regimen works. It's as safe as nine months of INH. I have also used this in my own practice.

There's one large trial in the HIV population that showed that this was also effective. I've used that trial to make myself feel better about using it in immunosuppressed patients. So far, at least anecdotally, in my clinic, I've probably used it in several dozen of these type of patients; and they've done quite well. I think if you've ruled out active TB and they have latent infection, I don't see why this regimen would be any riskier in someone who's on, or going on, a TNF blocker necessarily. I think it's a good regimen. Again, it's a lot easier to finish for some of these people. But again, you have to be aware of drug/drug interactions with rifapentine, et cetera.

I show this mainly in rheumatology talks to tell the rheumatologists just how smart they are. This was a study that looked at European countries; and this is the G5 countries, which I don't even know what that is. I'm just kidding. I think I know what it is. I think it's the biggest five economies in Europe; and I don't know who it is these days, but probably Germany and France and England, and I'm not sure who else. And these are the non-G5 countries. The bottom line is in all these countries, rheumatologists are fairly aware of TB screening guidelines. But rheumatologists, compared to GI docs and dermatologists, are doing a slightly better job in terms of being aware of the guidelines and following the guidelines. These are the percent of people who reported following guidelines in the survey. It's about 80% to 90% for rheumatologists, and it's about 10 points lower for the other specialists.

This probably reflects back to these drugs have been around the longest in rheumatology, and that subspecialty has really plowed the way in terms of helping develop screening guidance around using these drugs.

Let's talk about the other drugs. Rituximab, I told you already this is a virtual B cell depletion drug. What that means is you have essential B cells in your bone marrow, and you have peripheral B cells that float around. This takes all of those out. There was no TB in RA clinical trials, or really necessarily reported, in its use in B cell lymphoma. We did a survey a few years ago of ID specialists in the U.S., and we uncovered eight cases of microbacterium; some were TB, some were NTM. There's at least one animal model that suggests when you knock out these B cells, you do promote TB survival in the mouse at least. I think theoretically there's possibility that this drug does increase the risk of TB; although if it does so, it's quite minimal because we haven't seen it in human studies.

This B cell is part of the granuloma, and presumably it does have some importance in that setting; so again, I always think about it. I have seen some pretty odd NTM cases; we publish these cases. So I do think there's probably something here, but it's just not likely the risk that we see with TNF blockers.

Abatacept is the CTLA-4 ligand. This is that drug that gets between the T cell and B cells and other things that allows T cells to become active, but it really mitigates or dumbs down that response. There are at least 12 cases of TB reported in post-marketing data; the rate is 90 per 100,000. Of course, that post-marketing data is from open-label studies that have been conducted all over the world. So I don't really know what to make of that rate; I don't know if it's elevated or what it "should be." But the bottom line is you should screen patients before you put them on these drugs. Again, I think TB is possible.

There is a murine model that's looked at this, and abatacept did not -- distinct from the TNF blocker studies and the Rituximab study I just mentioned -- abatacept in mice did not influence the mouse's ability to control TB, so maybe this is a safer drug. We think about that actually with a variety of infections, and it's a thought; there is some data behind it. The data I'm showing here is the animal model I just mentioned. Up here in "A," this is the mouse survival; and you can see the thick line here. The ones on abatacept seem to do just fine, and the ones on TNF drugs all died pretty quickly. These were MTB-infected mice that were treated with both. The rest of these are just CFU counts, and they go along with the same story I just told.

There is one head-to-head RCT of abatacept versus infliximab that seemed to suggest the higher percent of opportunistic infection in the infliximab arm as compared to the abatacept arm. That included two cases of TB in this arm. I think from a population-based standpoint, we've looked at general bacterial infections; we've looked at opportunistic infections in the way of herpes zoster, which all these infections seem to be slightly lower in abatacept, although not by much. I do think there probably is some safety difference with regard to this type of infections between these compounds.

IL6 -- this is a cytokine that is an upstream, pleiotropic cytokine. I had to look up that word, "pleiotropic," years ago when I put this slide together. It means you do everything or you do lots of things to lots of things from lots of places. That basically sums up IL-6. It's secreted by a lot of different cells – T cells, macrophages, other activated immune cells; and it stimulates both TH17 development and B cell development. TH17 is a specific subtype of T cell, and I'll show you a diagram here in a second which should help you understand what those do.

If you look at animal data with TB and the IL6, in mice it's all over the place. These are all different types of infections; the TB is highlighted there. Some of these studies showed an increase in TB-related mortality in the mice when you blocked IL6. Some of these actually showed that there was no difference.

When looking at some of these other bugs, sometimes IL-6 blockade improves survival; and sometimes it hinders survival. It's really all over the place. My assessment is that it probably depends on when you inhibit IL6. If it's close to the time of infection, it may be very different than if it's a long time after infection.

Human data is as follows. We have a drug called tocilizumab, which is listed here at the top. This is the drug that blocks IL6, and it blocks the receptor to IL6. In population-based studies -- and this is again

long-term extension trial data, meta-analysis, and clinical trial data -- the rates of opportunistic infections were 230 per 100,000. And that's about the rate we've sees in various studies with TNF blockers. There were several cases of TB in that series. In Japan, where we have a good observational study, we showed -- we didn't show, but others showed the TB rate to be 220 per 100,000. This is very similar to the rate that we've seen in the TNF blocker studies there, also post-marketing; and it's about 10 times the background Japanese rate.

When I'm asked what this drug looks like, it looks pretty similar to the TNF blockers to me in terms of their ability to cause TB and actually some of these other infections, like pneumocystis and zoster. These are pretty similar rates as what we see in the TNF literature.

Now, if you look at in vitro studies and animal studies, however, the IL6 blockade doesn't seem to be as risky. I just showed you the animal data. It's kind of all over the place and uninterpretable. This is an in vitro study that was similar to one I showed you before that compared etanercept and infliximab and adalimumab. This was an in-dish study looking at interferon-gamma production stimulated from MTB antigens in patients with active TB, and they were exposed to these various compounds in the dish. The ones with tocilizumab in the dish produce a lot higher levels of interferon-gamma as compared to the ones with etanercept and then infliximab. In this level of tocilizumab -- I drew this red line here -- you can see that the control, the no-biologic group, and the TCZ group were pretty similar, and they're definitely higher than those with the TNF blockers.

This idea is that tocilizumab doesn't down-regulate interferon-gamma to the same extent, so maybe it's of less risk. Again, the human studies suggest it's pretty similar. This is the mouse model study that is probably the best study that looks at this. Again, this is new infection TB; these are mice that were given an inhalational dose of TB. This is distinct from the latent TB model. I wrote this here: Would a chronic TB or latent TB model give you a different result? It's possible because, again, IL6 is this immune modulatory cytokine; and it may behave differently early in the time course of infection as compared to later.

What this acute TB model showed was that the mice given the TNF blockers died pretty quickly. There's the survival curve, and the ones given the IL-6 blocker survived to a much greater extent. And these are CFU counts of TB in different organs, and you see similar differences. You see IL-6 is the black thing here -- I'm sorry, that's the control. The IL-6 is the white bar, and this is the TNF bar; so you can see in the TNF bar, there are much higher CFU bacterial counts than compared to IL-6 blockers and the control arm.

There is some suggestion here that the tocilizumab might be safer; but again, the rates we've seen in TB studies seem pretty similar. And again, I guess in the end it doesn't matter; it's a moot point. You need to screen these people before they start this drug, just like any of these other drugs.

The last few minutes here, I'll focus on a couple of other drugs of different mechanism. This is IL12 and IL23. There's a subunit called P40 that's shared between these two. When you have a naïve T cell, it either differentiates into a TH1 cell or a TH2 cell or a TH17 cell; these are some options for that naïve T cell. The TH1 response we know is very important for mycobacterium. The TH17 response is really important for candida, staph, extracellular bacterial; it drives neutrophils responses. But it may also have some importance in TB immunity as well, and I think that's been shown.

When you block T17, you can down-regulate these IL17 molecules, which then down-regulates responses that are really directly related to candida and staph aureus. Yet we don't necessarily see an increase in those infections in patients on this drug. I really worried about this drug. I thought we were going to see mycobacterial and salmonella infections. And why did I think that? Because when you inhibit this P47 unit, potentially you're going to inhibit IL12 and IL23; and IL12 is really important for this, right here -- going up to the TH1 response. IL23 is important for going down here; this IL-23. So if you're

blocking both of these pathways. -- again, really I worry about blocking this TH1 pathway --you're going to down-regulate interferon-gamma, TNF alpha, et cetera. You're going to get more TB.

We know from humans with IL12 or IL23 defects, P40 defects, deficiencies, auto antibodies, et cetera, those people get these types of infections. They get disseminated salmonella infections, and they get mycobacterial infections. But we have not seen that in patients on ustekinumab. There are really, to my knowledge, no cases of TB associated with this drug, at least in the clinical trials. And in the open-label experience of this drug, there are over 3,000 treated patients. Suffice it to say, all these patients were screened; so that is something that is important to recognize. Perhaps the studies weren't done in high TB endemic areas either. This is a different population than the RA population, which make up most of the studies I've mentioned or showed earlier. Bottom line is we just haven't seen the types of infections I was expecting, and I'm not sure why that's the case.

The Brave New World, to end this talk on a few studies of JAK inhibitors. I made the joke earlier, I didn't know jack about JAK until like two years ago. Now I know a lot about JAK, and I spend a lot of time thinking about JAK inhibitors. And these are kinases, intracellular kinases. You have JAK; you have Syk; you've got P38; you have MAPK. You have a number of kinases that sit in your cell that have receptors to the outside world. And when certain pathogens bind those receptors, it turns on JAK. JAK then makes STAT. and STAT goes into the nucleus and basically drives your intracellular machinery. It turns on DNA transcription; and it makes everything you need -- like TNF, IL1 and IL6. You produce new blood cells, et cetera. This is what drives your DNA replication in the cell.

We know that a number of inflammatory pathways and responses are mediated through the JAK receptor, and so there's been a big emphasis in trying to block JAK. People have also blocked Syk; it didn't turn out so well. The Syk inhibitors have been cancelled, at least as far as I know for now, due to infection. I don't think the P38 inhibitors have panned out very well in terms of efficacy. But the JAK inhibitors work really well for psoriasis. They work really well for rheumatoid arthritis. But there is a distinct infectious signal coming from those compounds. The only one that we really know about and that is published is tofacitinib, and this blocks JAK1 and JAK3. There are four JAK receptors, and this blocks JAK1 and JAK3. And these things go together at the cell surface; they form combinations or dimers.

I did this study. We looked at the clinical trial data from North America, Western Europe, and globally where these trials were run. And we saw a TB rate of 173 per 100,000. Most cases where at a 10 milligram BID dose, and the two doses were 5 milligrams or 10 milligrams; so we did see this dose-dependent signal. All these cases screened negative prior to trial entry. There was a pretty good length of time between trial start or drug start and development of TB. I think probably at least a good chunk of these cases were probably newly-acquired during the course of the study.

You can see these rates; it's hard to see, but we calculated the rates in the trial of the development program according to the background incidence rate of the country. We have low, medium, and high. The U.S of course is low; Western Europe is low. And this was defined as less than 20 per 100,000. But when you look at the rate in that group, the rate in the asociotofo was 0.037, or 37 per 100,000. It was elevated, but we had only one case from those regions.

The rate in the medium regions of prevalence, which was basically between 20 and 50 per 100,000, the rate was similar; it was 34 per 100,000. But the rate in highly-endemic areas, we have 10 cases in those areas, and the rate was 781 per 100,000. Those were mostly in China, India, and Southeast Asia. So I think the rate is elevated with this drug, and there does seem to be some dose-dependence associated with it.

The good news of the study was I really like what they did. We have not published this yet, but it was presented in a major conference. There were 209 patients diagnosed with LTBI due to screening at the start of the trial. All of them went on INH for nine months. And after one month, they started tofacitinib.

They all finished in nine months, and none of them developed TB; and no one had abatacept toxicity associated with their INH. So this showed that you can screen and treat TB while you put someone on this drug, and I think this is important.

The last bullet there that INH is the therapy of choice, you should know that rifampin and tofacitinib have a drug/drug interaction. Rifampin will cut down bio availability, so tofa won't be very active. So you probably won't hurt the efficacy of rifampicin, but you will hurt the efficacy of tofacitinib.

My conclusions—TB risk with anti-TNF therapies is clear. The newer biologics, I think it's a big question mark; but the animal data suggest less risk for tocilizumab and abatacept. But the human data suggests similar risk for tocilizumab and probably less risk for abatacept or rituximab. And the emerging data with JAK inhibitors suggests there is risk.

The bottom line is there in red: screening prior to immunosuppression. I don't care if it's prednisone or methotrexate or any of these drugs. When someone is likely to be immunosuppressed for a long time period, i.e., they're either newly-diagnosed with RA or psoriasis or something like this, I would take the time to screen them while they're relatively immunocompetent and understand what their TB status is. That's an important thing to do, and I think that's just something that hasn't been done historically. We're playing catch up. It's harder to screen these people once they're immunosuppressed. Our tests just don't work as well in that setting.

Screening in the biologics setting --these are my words to live by. Number one: a priori probability reigns supreme. This is how I think about it. This is very George Bush-like; it's pretty black and white. But if they should be positive, then they probably are; and if they shouldn't be positive, they probably aren't. That's how I think about it. And if they should be positive and they're coming back negative, I often repeat my test because I know they should be positive. I don't believe it. If they have risk factors, then use two screening tests to maximize your sensitivity, particularly if they're immunosuppressed. And again, if you don't believe your test result, repeat it. And that's true of any test in medicine; we're all taught that in medical school.

This is a partial list; my fellow and I published this article in *CID*. I think that there's another table alongside this, but it doesn't matter. You can see that it's overwhelming. These are all drugs in phase 2 or Phase 3 trials. Some of them are very close to approval. And just to show you that -- lots of names you can't pronounce, numbers, and hyphens and things like this; you don't know what they're going to be called. The bottom line is, again, immune mediated inflammatory diseases, such as lupus, RA, Crohn's, et cetera. You can see the different targets. We have a slew of anti-IL17 drugs coming, a slew of JAK inhibitors coming, and you have all these other targets, too: IL6 targets, IL21 targets, et cetera. This is an expanding field and it is interesting and exhausting to try to keep track of it.

Last, another shameless plug for NTM. This was a patient who was on infliximab, and he developed pulmonary MAI and was switched to etanercept, thinking it was safer. And they were put on four drugs for MAI. They just went downhill and developed large cavities and really behaved differently than most MAI cases in terms of really rapid progression and they died. This was Mike Iseman patient who he enlisted my help with, and so thank Mike Iseman for donating this slide. The point is, again, in the U.S., were just as likely or more likely to see NTM in this setting; so keep your eye out and be vigilant. There's really no way to screen for NTM necessarily. It's different than TB; it's not necessarily as preventable.

That ends my presentation. I'd like to acknowledge my friends that helped me with all this work, and Dave Askin and his crew in Florida here for inviting me. I'm happy to spend a few minutes taking questions. Thank you.

Kevin, that was simply outstanding. Thank you so so much. We have a couple of minutes for questions, Kevin, if that's okay with you. And I guess if it's okay, I'd like to start. We had a number of questions about

the whole idea of the possibility of developing, especially in high-endemic areas,TB while you're on therapy. A couple of participants were asking: what are your recommendations? And again, we're in a low risk area; but among higher risk -- I guess two-part question. Here in the U.S., do you continue to screen your patients on tumor necrosis factor blockers or biologicals throughout their treatment; and if so, how often?

Yeah, that's a great question. When I was at CDC, we wrote screening guidance around this MMWR time (inaudible) -- this was a while ago, it was like 2005 or 2006. And we did not recommend repeat screening. We thought people should be screened; and in the absence of risk factors for new infection, there was no reason to repeat their screening. I still feel that way. I think that's consistent with how we, as TB people, approach all settings in immunosuppression in the U.S. I don't know any setting where we're repeat screening people on a yearly basis in the absence of risk factors for infection. For example, HIV patients in Oregon -- we screen them once. We don't screen them again unless they're homeless or in jail or unless they have a risk factor potentially for being exposed.

My belief is that the same approach should be used here. I think most of the patients in the U.S. once they've been screened and their status is now on the go on these drugs, they don't need to be screened again in a year. Again, that's a soapbox issue. I get on it when I'm talking around the country to rheumatologists or dermatologists about this. That being said, there are some people that travel to India to see grandma; there are some people that work in homeless shelters; there are some people that are at risk and so if you're at risk for new infection, then some periodic repeat screening seems reasonable, particularly if it's pegged to the potential of exposure. That's something that should be considered with every patient.

I can tell you that the FDA labels for these drugs say that patients should be screened at baseline and then again periodically. And when they wrote that, I don't think they consulted us at CDC; that's my recollection. And I think a lot of rheumatologists feel bound by that label, saying, "Well, I have to repeat their screening." And so they do that. I often see people get into trouble with it because they end up with a false positive in year three. Some of my patients have been on infliximab for three years, and they grew up in Oregon and they've never left the state. Now I've got a positive IGRA or positive skin test. What does that mean? Well, it means you shouldn't have screened them. They were negative the last five times you screened them. Why are you screening them again? I think you can get into trouble screening people that don't need to be screened.

I agree, Kevin. And along those lines, a couple of questions also were asking about-- this was always a question with HIV. Everybody knew that once you're infected with TB, your chance of progressing from infection to disease was increased. But one of the big questions was, "What about if you are exposed? If an HIV positive individual is exposed to someone with TB, do they have a greater chance of going on to TB because, as we know, only about 30% of all individuals who are in contact with an active case traditionally become infected and go on. Is there any data whatsoever that patients of tumor necrosis factor blockers are more susceptible – meaning, if they are exposed have a higher chance of becoming infected and developing the disease?

So as this thing from someone who's got latent TB and is reactivating or progressing to active TB?

Right.

Yeah, that's an interesting question. There's certainly animal data that speaks to the answer being yes. If you're on TNF blocker and you're newly exposed, you are at higher risk of developing TB. That's a hard question to answer in humans. Outside of an experimental setting, it's often hard to figure out from these studies whether the people are reactivating, or progressing from latent to active, or if they're being newly infected. I think the answer is definitely, yes, because you can look at these studies where there are

patients from India and in other places and they develop TB two years after they're starting their TNF drug.

It's definitely plausible that that's a person with latent TB that has now progressed. But it's also maybe as likely, or more likely, that's a new infection. As distinct from someone who develops TB three to six months after starting one of these drugs, that's probably more likely, particularly if it occurs in the U.S. or somewhere where there's very little TB transmission going on. The chance they've been newly infected is almost zero. It's much more likely to be a case of progression from latent to active disease.

I think your question's a good one. There's really no experimental evidence to answer it. But I think intuitively, how we know how these drugs work and how they would interfere with granuloma formation and really are actually control -- I didn't get into the macrophage -- but really it's about control of the TB bacilli in the macrophage. I think the interference of that process in the context of a new infection would almost certainly argue that the patients are at risk in that way.

Exactly, I think even now though the HIV – it's still out there. You would hope that with all the data we're collecting, it may be better answered; but still, like you said, it would be very difficult.

Before we go any further, if anybody has any questions they want to ask Kevin live, we'd love to hear your voice. All you have to do is push "star 7" to unmute and then "star 6" to go back on mute. In the meantime, let me ask a question. And then once that question is open just cut in and say hello.

Real quickly, I think the burning question, Kevin, by far is the famous question all of us clinicians get all the time, which is: When do you start the tumor necrosis factor blockers? Because I think you'd agree, most of these patients are really, really ill and they are anxious to start. Traditionally, we've always talked about, well, it's always been up in the air -- anywhere from three to eight weeks, depending on if you're looking at the international standards.

Many people say one month but in reality, they're also –I know with the golimumab--- I botched that name; I did not practice nearly as much. I know in many of them, they started immediately; and they did okay. Any firm studies or anything that really looked at when is the best time to start?

That's a good question and a frequently asked question. Most of this one-month gap between starting LTBI regimen and starting a biologic, it's all come from that Spanish study; and I think most of us just adopted it because that was the evidence, that was the data. There are a variety of studies, including the golimumab studies I showed you, as well as there are other studies -- the Westhovens study. And there are a number of studies now that have shown that's not necessary. You can start these things simultaneously. So I feel very comfortable that that's the case.

But I can tell you that functionally, it's always nice to know someone's actually picked up their INH or rifampin or whatever you're using and actually start taking it. I do argue that some sort of gap is useful, and that's really to make sure someone's actually taking their medicine before they start one of these drugs.

I have had patients who have started their TNF blockers; they come back four to six weeks later for a follow-up visit, and they haven't even started their INH yet.

And I'm saying, "Gee whiz guys, I thought you started this a month ago."

They say, "No, I just didn't pick it up."

So I like to know that they've started it. So I think some gap of two to four weeks is very reasonable. Actually, it almost always plays out that way because people have to get approval to use these biologics. They're very expensive. It often takes several weeks to arrange; so usually, there is a gap even if you didn't want one.

Towards that end, we have a couple of questions about INH and rifapentine. I guess the question is: Do you still wait even one month with the INH or rifapentine, especially since one advantage in some ways right now is the recommendation is for INH or rifapentine to be given by DOT. There is kind of an advantage that you will know that those patients are taking it. Do you still, Kevin, in general, wait a month when using that regimen?

Again, I think functionally the way it plays out is generally there is some gap. I don't know any data. No one has studied this, so I can't tell you like I can with a daily regimen, like the example from the golimumab trial that it's okay to do. I think theoretically it should be; and I think some sort of gap, again, makes sense. The way I do it in my practice, I usually start people; and I have their first dose observed. And then I say, "Okay, you can go ahead and start your biologic." And it usually takes a few weeks before they can get it, so there's usually at least a couple of weeks' gap.

I do like to know that they're tolerating the 3IR. Not all my patients tolerate it. I'd say 15% to 20% of them have significant fatigue surrounding the rifapentine dose for the next 24 to 36 hours after they take their weekly dose. I've had a number of people quit the regimen because of that, and a lot of these people are older individuals, so not everyone is willing to go forward with that. I kind of like to know again that they're on it and they're willing to keep taking it before they start their biologic. So I think some gap of at least several weeks is useful for that.

I agree. I totally concur with the side effects for the INH/rifapentine. But it's always amazing when I say, "Well, okay your alternative is nine months of INH," how quickly that fatigue just clears up.

Towards that end, a couple of people say, in your experience, who ends up treating these LTBIs? Is it the treating physician, like the rheumatologist or dermatologist; or are they getting referred to the Health Department--

I think few of them go to the Health Department. I mean, I treat a lot of people like this; and I have colleagues that do. I think a lot of these people get referred to ID or, in some cases, pulmonary -- particularly from the dermatologist. I think the rheumatologists, some of them will certainly treat the LTBI themselves because they feel comfortable doing it. The dermatologists, I think, are less comfortable; they're not internist like the rheumatologists. So I think probably just from a background standpoint, they're more likely to refer.

I appreciate that, Kevin. For a second now, let's just wait.

Anybody want to ask Kevin a question live? That's "star 7" to unmute. I know Mark Labado is on. He has a question, and he always like to speak.

Mark, are you there?

Well, Mark's question was -- I'll ask it for him. In your example about your high risk patient, you talked about using both the IGRA as well as the skin test. His question is: In that example, would you use two IGRAs -- because that was kind of what you talked about, meaning the T-SPOT and the QuantiFERON – or just one?

That's a great question.

Don't give Mark credit for a great question. If he didn't ask his live, he gets no credit.

Okay. It's not a great question Mark. But I think it is something to think about, and here's what I think. That French study I mentioned -- this is essentially what they did. They used a skin test and both IGRAs, but they ignored the skin test result. And they ignored it because almost everyone in that study had a BCG history. So what they essentially did was a dual IGRA screening approach. I definitely advocate that in people who have a history of BCG, who are immunosuppressed, and have risk factors for TB.

The example I gave, which I think he was asking about, was my guy from the Philippines, which you know I used a skin test and I used QuantiFERON, and I did so at the time because I don't think I had access to the T-SPOT. Now having access to it, if I did that over again, I might have used both IGRAs instead because I do think that's a very reasonable idea given the gentleman had a BCG history. So that's a good question and a good thought, and I agree with Mark on that.

Don't say that. But towards that end—Here's my question to you-- practically, a lot of these patients are coming to you on prednisone or on other agents. And what I've found in a number of these cases when they're coming to me is that when I go to do the QuantiFERON, I get indeterminate results because their mitogen is low. So I guess here's my question to you: Do you see any advantage – and, again, this is not one preference for one test or another -- but do you see any preference in like using the T-SPOT over the QuantiFERON, or do you see similar results? Or, again, you're doing both; but in those kinds of situations with an indeterminate, do you think maybe going to a T-SPOT just to see what you'd get could be an advantage?

Yeah I think if you look at the data and the studies, where both those type of tests have been employed in a screening test if you will, that most of the time they concord pretty well. Of course, there's no gold standard; so you don't know who's right and who's not right in these individuals where there's discordance. But most of those studies, they concord pretty well.

If I had to be pinned down, I'd say maybe the T-SPOT's slightly more sensitive; but maybe it's also slightly less specific than the QuantiFERON. That would be my kind of assessment from looking at all the literature across all settings. But from a clinical standpoint, I think they're very similar; and I don't really distinguish between them. I think if you get an indeterminate test on the QuantiFERON, I think repeating the test with a QuantiFERON or a T-SPOT or a skin test -- these are all reasonable ideas. I mean, you should repeat that test. And picking the same or different method to repeat, these are all reasonable approaches; so I would advocate any of those.

I really liked your slide, Kevin, a lot about clinical. You know you can increase the performance of these tests by your pretest probability. I think a lot of us just don't think about the pretest probability enough because it really enhances the positive predictive value. I guess I would ask you this, Kevin. You made a statement, and I think all of us are stuck in this. So I get somebody who comes from a high-risk country; and I'm about to start a very, very potent immunosuppressant. Do I really have to do the test? I mean the bottom line is how often are you just going to start because you just feel that this test is going to be "falsely" --

That's a good question; and it gets back to, again, my Philippines guy that I've talked about. I mean, I ended up just treating them empirically anyway; and I ignored these negative test results because I didn't believe them. This would be consistent with the 2006 British Thoracic Society Recommendations, which were just that; if someone comes from a place where it's likely that they have TB, why even screen them? Just treat them empirically. That's not an unreasonable approach.

I still think you should screen them because I think it's good to know what they're screening tests are, or were, because it helps you understand and potentially interpret future screening test results. So I would get them; I disagree with the BTS guidance in that regard. But the idea of, gee, they are at high risk -- I

don't really believe the screening tests because they're immunosuppressed; I'm going to treat them anyway. It's hard to argue with that.

I've done that before, like the example I gave. It just depends on what you think their ultimate risk is and what the patient is comfortable with. I have to say having the new 3IR regimen -- it makes treatment easier, and it makes your chance that they're complete higher. It may push me towards treating more people because of that -- because that benefit risk equation may be slightly different.

Obviously I totally agree with you. There's also some information you actually may get from the QuantiFERON entities. That actually may be helpful; it does give you some indication if the T cells are responding. Now, what clinically that means, we don't know. It's trying to give you some information.

I should add one more thing, Dave. When you asked the question about repeat screening -- and a lot of people repeat screen people, like we discussed. But a lot of times, they use one of the IGRAs. And I just want to put that out there that that's fine; and that's what I would do too if I was repeating someone's screen test. But TNF blockers down-regulate the responses that those test measure. There is data; there are four or five studies now that suggest that you do see false negative IGRAs in patients who are already on TNF blockers. So that always something I think about when I have a patient who is being screened and they're already on a TNF blocker, so it's something to keep in the back of your mind.

Definitely. And again, you do get some sense of that too when you do these studies. When you're looking at those mitogen responses, you really do see them drop off once they've started if they've been repeated.

I guess one of the big questions we're getting -- because we're running out of time -- is pediatrics. We talked a lot about adults; but in kids who are going to be started on some of these agents, especially those with like juvenile rheumatoid arthritis or other issues, do you use the same screening? And are you seeing kids being started on these agents?

Yeah, I mean certainly kids do get these agents; it's pretty rare though. I mean JI is pretty rare. Most of these kids are born in the U.S. Most of them have no risk factors. So the risk for TB is pretty low, just knowing all that. They should still be screened. I always say that if you want to screen a kid for any reason, you ought to use an IGRA and a skin test; you should use them both. I mean, if you really want to know what a kid is, you should improve your sensitivity to your greatest degree because none of these tests are probably as sensitive as we want them to be in really young children. So I would dual screen a kid, particularly if they have risk factors. If they have no risk factors, I would be less excited to do that. But, again, most of these kids aren't under age five. I don't know of kids under age five are getting these types of drugs. You'd have to ask the pediatric rheumatologist; but I haven't run into that because most of these entities occur later in childhood.

Kevin, I cannot begin to thank you. And on behalf of all our listeners, we so want to thank you for such a great presentation today. It's one that I'm sure everybody will – and if they haven't already faced it, they're going to face it real soon. Kevin, thank you so, so much. We can't thank you enough.

For those questions that weren't answered, if you still want the answer, if you just would email us. We'll get that to Kevin or one of us, and we'll try to answer your question.

Other than that, Kevin, thanks again for everything.

Megan, I'm turning it back over to you. Maybe I'm not.

I'm sorry; I'm here. Sorry about that Dave.

Go ahead.

Yes, we just want to thank everyone for attending today's grand rounds webinar. Please remember to complete your evaluation by the close of business.