

A Practical Approach to Using IGRA in Diagnosing TB

August 13, 2013

Dr. Robert Belknap

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We're so happy to have you. As you know, many of you remember a couple months ago, back in April, we were all together talking about PPD shortage, and at that time, during the webinar, it became obvious that more questions were coming up about IGRAs and their use during that webinar than actually about the PPD. And, you know, we did the webinar. It was, you know, well received, and we kind of thought we were out of the woods. As you know, the Tubersol and Aplisol issues seem to have been getting better, and, you know, we were working on the IGRA, but we didn't feel that same, you know, pressure that we had to get it out. But, you know, we knew it was very, very important.

But what was very, very interesting, in the process of getting this IGRA webinar together, as you guys are aware, yesterday the CDC put out an advisory again making us all aware, as many of us had already been experiencing, that the PPD shortage was once again upon us. And then again, Tubersol was now in short supply and Aplisol, because of demand, was hard to get. And I have to say, as you're aware, it's amazing how timely and the appropriate timing of this webinar today is, because I think, given the recent events, and now the events we're facing now, we really need a practical approach to IGRAs and how they're being used and how they can be used, and that's why -- I mean I am so, so honored today to have Dr. Bob Belknap, who is going to join us today to give his presentation on the practical approaches of IGRA.

As you guys know, Bob is the director of the Denver Metro TB program. He is also the president of the National Society Of TB Clinicians. Bob also serves as the principal investigator on the Denver TB epidemiologic Study Consortium, as well as the TB Trials Consortium. And, as you know, both groups have been intimately involved in studies looking at latent tuberculosis infection, and it's diagnostic techniques. And, as you know, Bob is the co-chair for the TB TCL TBI working group and protocol team, and I think we're in for a very, very, very practical good lecture, but I think you'll also agree that many of you, as you found out that the last time, are going to have a lot of questions, and that's why, at the conclusion of his presentation, we're going to have time today for Bob to answer your questions, as well as we're honored to have joining us today, our colleagues from the CDC. We have Sundari Mase who is going to join us to help answer some questions. She's the medical team lead with the field services and evaluation branch of the division of TB elimination, as well as Jerry Mazurek, as anybody who has done any work with IGRAs and looks at the literature, Jerry's name is all over it.

As you know, Jerry is the captain in U.S. Public Health, as well as the medical officer with the Clinical Research Branch and the division of TB Elimination. And I have to say, I know I say this every time, how excited I am, but I am unbelievably excited for today's program. And, Bob, I can't say enough. I put all this pressure on you. It's all yours. So without further adieu, Dr. Bob Belknap. Thank you, Bob, for doing this for us.

Thanks for that introduction. Yeah, a lot of pressure, I'll do my best to live up to it. So as the title of the talk is listed, "A Practical Approach," I have no conflict of interest, but by way of disclosure I'll say that the opinions here are mine. This is not going to be an exhaustive review of the literature. It's also not going to be a comparison of the two available IGRAs on the market.

The goals of overall that, hopefully, you'll take away from this talk are that you'll be comfortable really describing and applying the current recommendations for using the interferon gamma release assays, integrating them in various clinical situations, and then disseminating some programmatic experience, and we'll go through that, largely through some cases where you all will have opportunities to give an answer for what you would do next in scenarios that we've experienced but, I think, are very common in practice overall.

Some more sort of specific objectives I would say is that, you know, I hope that, after this talk today, you'd be comfortable listing what are some of the benefits and limitations of the IGRAs in patients with different TB risks, so from the suspected active TB to special populations, including HIV-infected persons, in

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children, and differences and benefits and limitation in high-risk groups versus lower-risk groups for TB infections.

We'll go over some of the operational advantages and some of the disadvantages to using IGRAs, and then a little bit into cost issues. First, regarding the tuberculin skin test, and this is something that I'm sure you all are well aware of, is that the limitations to the TST, certainly the subjective interpretation, difficulty maintaining proficiency. It requires two visits. It's affected by the BCG, and then a limitation that I felt has been problematic, and that is the fact that primary care providers just don't like it. As much as I think we talk about TB prevention and we know that TB prevention -- what we can do at the Health Department is limited. Many of the people who come in with active tuberculosis had been seen by a primary care provider. They could have been diagnosed with LTBI and there was a missed opportunity. And part of, I think, is the TST. People just don't have confidence in it. It's difficult because of the two visits.

And lastly, you know, despite the fact that it's been used for over a hundred years, we've still never figured out a way to actually record the results so you can find it again. And so anyone who has tried looking through a hospital chart to find a skin test that was placed on a patient during a hospitalization knows the frustration, and that information is lost typically.

So along came the Interferon Gamma Release Assays, or IGRAs, blood tests for detecting TB infections. One of their huge advantages over the skin test was the fact that it did require a single visit, and oftentimes patients in primary care and other settings are already having blood drawn, so all it is drawing a little bit of extra at the time they're already having that done. The results are retrievable electronically, and I think it's hard to really underestimate the value of that. To be able to go back and find results weeks or months, or even years later, I think, is important and valuable for patient care.

There are two FDA approved tests, so the T-SPOT TB from Oxford Immunotec, and then the QuantiFERON TB Gold, originally developed by Cellestis, subsequently purchased by QIAGEN. So a little bit about QuantiFERON, again, Cellestis is the company out of Australia that developed this test. I always find it fascinating that it was originally developed to do a better job at testing cattle who get infected with *M. bovis*, and this is a very expensive proposition where they skin test cattle, and if they test positive, they end up killing the entire herd to prevent the spread of *Mycobacterium bovis*. And as you can imagine, in cattle you get false positive skin tests just like you do in people, so they started out looking for a better tests for cows and figured, well, if it works for cows, you know, maybe it will be okay for people.

The first test, the first generation of this, the QuantiFERON, was using PPD. All of the subsequent generations are similar in that they use whole blood. They stimulate them with antigens, and it measures interferon gamma that's produced. There's a nil, considered a control, and a mitogen that shows you that the people can actually respond, so it's similar to testing for anergy in a way. So the second generation of QuantiFERON was an improvement in that rather than taking sort of the large milieu of antigens that are contained in PPD, it was narrowed down to ESAT 6 and CFP 10, and then subsequently, in the third generation, the QuantiFERON Gold In-Tube, the antigens were put into separate tubes, and with that version, they added TB 7.7.

T-SPOT differs mostly in the laboratory technique that's used. It was a test that was developed in England. It's what's called a "modified LE-SPOT platform." And with this, the test is actually measuring interferon gamma production from effector T cells after you've separated out peripheral blood mononuclear cells. So you collect the blood, you separate it out, these PBMCs, they get washed, they get stimulated with the same antigens, the ESAT 6 and CFP 10, and plated, and then you can see in the picture in the corner, each of those spots actually represents a cell that was producing interferon gamma in response to that. The T-SPOT was approved in Europe in '04, and then the U.S. in 2008. The QuantiFERON, I didn't mention, was originally approved, the first generation, back in 2001.

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Basically they're fairly similar. So both require single blood draw, both incubate the blood or the cells with antigens from what's called the "Region of difference 1," or "RD1," and this is important, because those antigens are not contained in BCG. They are, however, present in *M. bovis*, so if someone were infected with *M. bovis* they should have a positive test. There can be cross reactivity, so these same antigens, the ESAT 6, the CFP 10, are contained in *Mycobacterium marinum*, *Kansasii*, *Solgi* [ph], and *Fulvacin*. So someone who was infected with one of those and got tested would, in theory, have a positive result. And the results, both can be available within one day, depending on the laboratory and how frequently they're running the test.

Some minor differences in terms of the results and how they get reported, so QuantiFERON, a positive test is a value that's greater than equal to 0.35 international units ML, and a negative is less than that. You can also get an indeterminate result. So an indeterminate occurs either because there's a low mitogen, so that's where there's an antigen in there that should just stimulate everything, and if that doesn't work, if you don't get stimulation, then the test isn't valid. So, again, that's sort of an anergy control if you will.

The other way you can have an indeterminate is if the nil value is too high. So if essentially there's too much interferon gamma in the tube that there should be little or none, then, again, it's you don't have an interpretable test and it's considered an indeterminate test. For T-SPOT they call it "invalid," but it occurs for the same reason. And the best way, I think, to think about an indeterminate result a lot of times is it's similar to putting a skin test on someone and they didn't come back. It's not that useful in terms of the information that you glean.

It is true that people who are immune compromised, so advanced HIV or very young children's whose immune system hasn't had time to develop, are more likely to have indeterminate results, but it doesn't tell you anything about what's the likelihood that that individual actually has TB. And then there is also a failed category for both QuantiFERON and T-SPOT, so if you don't get enough blood, if the tube breaks, if the blood doesn't get to the lab in time for the incubation, then it can't be run, and you could just have a failure.

Now T-SPOT has an additional category called "borderline." So borderline for T-SPOT, you can see, is anywhere between five to seven spots. Negative being four or less, and positive being eight or more. This is actually unique in the U.S. and was a category that got added essentially when they were applying for FDA approval. The approval in Europe and most of the world is actually a cutoff of six spots. So six or above is positive, and below six being negative. A lot of people have talked about this borderline zone and wondered whether or not there should be a borderline zone with QuantiFERON and would that, in fact, be helpful. And it has to do with what's been observed, and we'll get into a little bit, that there is variability so when you draw these tests in people, in the absence of treatment or in the absence of other things, there's some degree of change where people, the values will change a bit, and for some percentage of people, that change can be enough to make them go from positive to negative or negative to positive.

My own opinion on this is that a borderline zone from a practical perspective is not that helpful, because in the end you've got to make a decision, what do I do with a borderline. Either I go, okay, well it's borderline but they're high risk and I'm going to call them positive and I'm going to treat them as positive, or they're borderline but they're low risk and I'm going to treat them as a negative, and you go the route of negative. Or do you repeat all borderlines? I don't see it as being a tremendously useful category for T-SPOT, and I haven't yet been convinced that there is a good window that should be applied to QuantiFERON at the borderline range.

So a little bit more about the indeterminate test, what should you do with this? This is one, and there are many, that have looked at the results of indeterminates and how frequently they occur and what to do

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about them. This was a retrospective review from the Chest Clinics in New York City where they were using QuantiFERON. You can see, out of 28,000 tests, they only had 522 that were indeterminate, about 2%, and that's a range that's been reported. It's usually 1 to 2% of the time labs will get an indeterminate result. You know, if the lab is seeing more than 2%, then that's a problem and might raise a red flag, either about the processes the lab is doing or some step in how the blood is being collected.

It was fairly evenly split in this group in terms of the reason for indeterminate, so about half of those were due to low mitogens. And when they looked at that group specifically, the low mitogens were more common in younger age, so less than ten, females; Asian patients, and those who were U.S. born. And then about half were indeterminate because they had high nils, and a high nil was more often associated with being foreign born and/or being Hispanic.

When they repeated these tests they actually got valid results in 68%, so over two-thirds or just about right around two-thirds would get either a positive or a negative result by simply redrawing the same test. And that's what's recommended, and that's what we do in Denver. If we get an indeterminate result, our first step will be to repeat the test.

In other examples, including in this retrospective review, they show that some of the patients ended up getting skin tests as well, and most of them are skin test negative, and so a few percentage are skin test positive. The trouble with the skin test is if it's negative, you don't know if it's negative because the skin test failed or if it's negative because they really aren't infected, and so you always have to interpret that a negative skin test in, I think, this situation with a little grain of salt.

So we've got these two new TB diagnostics. They've been around for a about a decade or so. And the problem we've got is how do we evaluate a diagnostic test when we don't have a gold standard? And the answer, or at least the results so far, has been is that we have hundreds and hundreds of studies and really dozens of meta analyses, and as I mentioned, I'm not going to review the hundreds of studies, or even the dozens of meta analyses, but I have tried to select, I think, some of the ones that I think help to understand the performance of these tests and some specific ones that will help illustrate some points.

So if we just look at the number of guidelines -- and this was back in 2011, and the numbers have increased since then -- there were 33 guidelines from 25 countries, and they differed by country and within country, the recommendations differed based on patient risks. Just, in general, the approaches that different people have taken is some countries have recommended two-step testing, so do the skin test first and then follow it with an IGRA to confirm a positive test. Some have said IGRAs only just replace the skin test completely. Some have said use both, so in certain populations use IGRAs and in other populations use the skin test. And then the approach, largely, that has been taken by the U.S. and through the CDC's recommendations is use either the skin test or the IGRA, but in most circumstances you don't need to use both.

The most recent guidelines for the use of these tests was published in 2010, CDC guidelines, and in that the IGRAs were the preferred test for BCG vaccinated patients and then groups with historically low return rates for the skin test reading, so where you really feel like you need a result but the likelihood of getting the person back in two to three days is low.

So now we'll get into our first case. This was a 52-year-old male, originally born in the Pacific Islands, had some history of international travel in the U.S. Military. He was BCG vaccinated as a child, and he came into an emergency department complaining of cough for a month. And there's his chest X-ray, and it wasn't particularly subtle and it wasn't missed. He had diffuse infiltrates, sort of fibronodular in appearance, and it was identified as being an atypical X-ray. And so my question now for all of you, so certainly you're going to collect AFB smears and cultures, what else would you do in trying to diagnose this person? So your options are skin test and IGRA, both, or neither.

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So, Bob, I think one of the things that's cool now is technology. As you can see now, everybody is coming in pretty quickly here. And I think it's coming in very -- I would say, very much towards it looks like IGRA. What do you think?

It does. Now I'm not sure if that's a reflection of the fact that this is a talk on IGRAs. You're a good test taker. You know, that's always the most important things.

Yeah, that's right. I should have mentioned the beauty with all of these options I'm going to give you is there is no right answer, so whatever you would do is fine. It does look like the majority of people would choose an IGRA. Although 5% of people said, you know, this is a high-risk person, I would do both, because we really want to try and definitively diagnose this patient.

So let's talk a little bit about what is the sensitivity. Now I don't know if everyone's still seeing the poll. I can't -- it's still in my view.

Everybody is still seeing the poll. Would you like that removed?

Yeah, go ahead and take that away. So let's talk a little bit about the sensitivity of the IGRAs for active tuberculosis. And, again, as with a number of the questions that we're going to cover, there have been a lot of published literature, and typically, a lot of, then, meta analyses where folks have taken data from much smaller studies and tried to combine it, where no single study maybe was able to answer the question. And this is one that I liked. It was published. Roland Diehl was the lead author and was published in April of 2010. And in that, the analyses were limited, in some of it, to the commercially available assays, so the QuantiFERON Gold In-Tube and to the T-SPOT and looking at the skin test, and you can see the sensitivity there. So skin test was about 70% sensitive in this analysis, so 30% of people with active TB would be missed; QuantiFERON Gold In-Tube was a little bit better, it was about 84%; and T-SPOT had the highest sensitivity at right around 90%.

In a second meta analysis, and this was limited to low and middle income countries, and actually one of the nice things that was done here was that there was -- from a statistical perspective there was a higher priority given to studies that were looking at TB suspects, so similar to the case that we saw, a person coming in and you don't know they have TB. A lot of the other published studies have taken people with a known diagnosis of TB and then gotten their test, as opposed to someone who presents with symptoms that could be TB and then see how the test performed. So if you do that, and in this analysis limiting it to low and middle income countries, the skin test gets a little bit better in non-HIV infected, so about 78% sensitive. QuantiFERON and T-SPOT were pretty similar to what was seen in the previous meta analysis.

But what was also included here was the comparison of non-HIV versus HIV, and, you know, certainly not surprising, but it's always interesting that to be able to quantify to some degree, all of these tests performed worse in HIV-infected patients. And so, you know, the answer is that the interferon gamma release assays maybe appear a little bit better. They're still not sensitive enough that in someone who is symptomatic and at risk for tuberculosis, that this should be a test that determines whether or not you start empiric TB therapy in and of itself.

So what happened with our patient? So it turns out he actually was previously skin tested negative. He got evaluated at the hospital. He had a negative QuantiFERON Gold In-Tube, a lung biopsy that showed granulomas that were AFB smear negative, and, unfortunately, the Health Department was not notified and he was given a presumptive diagnosis of sarcoidosis and put on high-dose steroids. And he died a month later from progressive pulmonary tuberculosis, and that's his X-ray when he represented to the hospital on those steroids. So, really, the worst possible outcome that occurred because people

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misinterpreted the sensitivity, really, of a QuantiFERON, but also the sensitivity of a smear, assuming that a negative smear and a negative QuantiFERON was enough to rule out active disease.

The next case is a 43-year-old female with rheumatoid arthritis, and so she was originally born in Mexico, had been BCG vaccinated, was currently on Methotrexate and low-dose Prednisone, and was being considered for a TNF alpha blocker. And so her rheumatologist did a skin test, and the skin test came back at 23 millimeters. I say "by report," because we didn't read it in our clinic. They sent the patient to us with that information. They followed up the skin test with a QuantiFERON, and the QuantiFERON was negative, and so that's why they referred the patient to us. They said, We've got these two results that disagree, now what do we do?"

So I'm going to ask all of you, you've got a patient, 23-millimeter skin test, QuantiFERON negative, what would you do? The options are to repeat the skin test, repeat the QuantiFERON, do a T-SPOT, or just treat for TB infection.

You know, Bob, we're really seeing more and more of this with rheumatoid arthritis, especially with the Tumor necrosis factor blockers. And I think one of the biggest issues that are happening now, you're seeing a lot of groups of specialists, particularly like rheumatologists who are not that familiar with tuberculosis now being, you know, put in a position to have to use the different tests and the confusions, and I find that's really, a lot of times, is making the water even more murky. Now you have a group of people being told to test but they're not so sure with what to do with the results. And what drives me nuts is the television commercials, which are just saying, "Just ask your doctor to test you for TB," like it's that simple, you know.

Yeah, I know. I know. I agree with you. We're seeing more and more of it, and I expect that as additional biologics and new therapies become available it's only going to increase, and so, you know, this is a good example of exactly what we see typically. Now I'm not seeing the results. Did we get the poll up?

Right now it looks like that about 70% of individuals are saying that they would treat for TB infection.

Okay.

About 15% are saying they would repeat the QuantiFERON. About 11% are saying that they would switch and do a T-SPOT. And about 5% that are saying they would repeat the skin test.

Okay, great. That's what we like is a nice mix. Well let's talk a little bit now about the BCG vaccine and the IGRAs. And so, again, this is from a meta analysis published in 2011, again, Roland Diehl was the lead author on this. And there are -- we could really pull out dozens of studies that have looked at this, and looked at the performance of these tests compared to the skin tests in folks who have had a prior BCG vaccine. And this is one of the areas where I think there is, in fact, the best data for the performance of the IGRAs. And so really fairly consistently the skin test is associated with being vaccinated, regardless of the TB exposure risk, so taking people from even low and medium burdened countries for TB in terms of TB incidents, but where countries that still use BCG vaccine, you will find rate of positive skin tests that really don't make sense epidemiologically for infection, whereas when the same is considered for the IGRAs, there's really no association with having a BCG vaccine or not and having a positive IGRA.

And this is sort of one example of that where they took 316 BCG vaccinated skin test positives, so these were all people with a positive skin test, and they got QuantiFERON, and they found in this group about 43% were QuantiFERON Gold In-Tube positive. And when they looked at the factors associated with it, so older age, having a larger skin test, being born in a high-burden country, being less time in the U.S., and in this case, male gender, were all associated with having a positive QuantiFERON.

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So, for the most part, things that we would consider risks for TB, including, as we know, a larger skin test is more likely associated with true infection and greater risk if untreated for progression to active disease because it probably represents true infection, so the 10 to 14, versus the greater than 20, really are different from an epidemiologic risk perspective. And this is important, I think in part, because we know that it's foreign-born persons making up an increasing percentage. Now it's up above 60% of our active TB cases are among people born in high-burden countries, most of whom have actually been BCG vaccinated.

The good news, I would say, is that when we look at how long these people have been in the U.S., most of them have, in fact, been in the U.S. for a year or more, which means there's an opportunity for us to diagnose them and prevent their TB. And so from a prevention standpoint, it says if we can find these people and identify them correctly, we've got a chance to prevent their TB, and arguably, and, again, I think the best data is that this is where the IGRAs perform well. And as we already showed, the CDC believes that too. In 2010 that was the recommendation. BCG-vaccinated patients, IGRAs perform better.

So what did we do with our patient? So she was QuantiFERON negative. I told you that her skin test was by report, and we're notoriously suspicious of tests that we don't do here and wonder if people read erythema and not induration, and so we said, "Well if you're willing, we'll redo the skin test on your other arm." We did that and it came out as 27-millimeters rather than 23, and so I talked to her and I said, "Listen, you've got risk for infection having come from Mexico. You've got risks for progression in that you're going to go on these TNF alpha inhibitors, and we've got these discordant tests. My recommendation would be that we treat you for latent tuberculosis."

I put up there the value on this patient's QuantiFERON test, so the TB antigen minus nil was 0.09, which, again, when we talk about, you know, borderline, so the cutoff being .35, some people have talked about .2 as being a borderline low or, you know, negative but near the borderline, and this person was not near that cut point at all. And she agreed, and we treated her for latent TB.

So the next example, a family from Nepal; a father, mother, and three children, children are aged two, four, and seven. All of them have been BCG vaccinated at birth. How would you test this group? Your options are skin test for everybody; IGRA for everybody; IGRA for the adults and skin tests for the children; IGRA for the adults and the older child, and skin test for the younger child; or something else?

And, Bob, this has really been an area that's really rapidly developing. I mean a lot of the early work on IGRAs was done more in adults. But now we're starting to get some information, more and more on its performance in children, and I think this is an area that we get a lot of questions about.

Absolutely. And, certainly, it was identified back in 2010 in that CDC document that this was a group where there just really wasn't a lot of information yet. But in the three years since then, there have been quite a large number of publications looking at these tests in children.

Which is always interesting, because to the point that you look at the Red Book, some of the information recommendations there currently are a little behind and don't reflect the new information. That's why I think this presentation is so timely.

Well right now, Bob, it looks like you have that approximately 48% or 49% are saying they would do IGRAs for the adults and for the older child and TST for the young, which I think is the traditional approach; and IGRA for all is 37%, close; and IGRA for adults and TST for the children.

Great. So let's go into that a little bit and talk about what is some of the information on the performance of IGRAs in kids? And so this was a study looking at the skin test versus T-SPOT, and prospectively 193 children tested with both tests, and what they did, and what many others have done in studies, is try to

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stratify the risk. So in the absence of having a gold standard, and when you're comparing two tests, you try to use some surrogate, and in this case and in many, the surrogate is the history of exposure, and so they had a mix out of these 193 children that had no risk for TB exposure, children that had risk but no known contacts, mostly foreign born but didn't have a known contact with a source case of TB; children that did have contact with a known TB case; and then children who had active TB. The median age was 8.6 years, but the range was as low as one month and up to 18 years.

And just, again, summarizing this, when they looked at multi-varied analysis they found that the skin test was really only associated in that with having a prior BCG vaccination, whereas T-SPOT was, in fact, associated with those different gradients of exposure risk. A study that's not yet published but was conducted through the TB Epi Studies Consortium looked at the skin tests and IGRAs in BCG-vaccinated children who were applying -- you know, coming as Visa applicants to the U.S. with their families, and so you can see that the countries where these tests were done, between Mexico, the Philippines, and Vietnam, and when we stratified that by age, you can see with the skin test, in the two to five-year-olds, 20% of them were testing positive, and then it did increase with age, as you would expect. You would expect, as children, you know, as you spend more time in a country with TB your risk of being exposed and infected goes up, and it did go that. It went from 20 to 25 to 30. But it didn't make a lot of sense that one in five kids age two to five was infected, certainly not based on the rates of active tuberculosis among that group.

We looked at the QuantiFERON in those same populations. It was 3%, 4%, and then 8%. And so, again, I think it provides some at least circumstantial evidence, in the absence of a gold standard, to say, "Boy, these tests are probably performing better," and we sort of would expect them to. Again, we know that in BCG vaccinated adults the IGRAs perform better. There's not really good reason to think that they would perform worse in kids who have actually been more recently BCG vaccinated.

Again, turning to the meta analyses, when they looked at this, so combining multiple tests, essentially the data is not quite as clear. That there are some similarities in the skin tests and the IGRAs in terms of exposure risk. The sensitivity and specificity for active TB was slightly higher for the IGRAs, but it wasn't statistically different. And overall, the accuracy appears to be similar. And so what we have really gone to doing in these patients is all BCG-vaccinated down to the age of two, we'll test them with an IGRA, so we'll draw blood and test them. Under the age of two there's less data. It's also harder to draw blood on really young kids, and so in those cases, those skin tests, for some practical reasons, becomes easier to actually perform.

The next case, this was a 20-year-old student, originally born in India, and some of the universities here in Colorado, because they have had -- primarily universities that have had cases of active tuberculosis and prefer not to go through contact investigations and all of the challenges associated with that, some of them require TB testing at college enrollment, and so he was required to get a test, and he got a skin test and it was 11 millimeters, and he had a chest X-ray that was normal. And they offered him LTBI treatment, and he said, "You know, I don't need it. The skin test is positive because of my BCG vaccine," and that's not unreasonable based on what we just looked at, 11 millimeters is a small positive. It's very possible that this is a reaction related to BCG.

So they did a QuantiFERON on him, and his QuantiFERON was positive, and the value -- you know, the antigen minus the nil again, was 1.15, so reasonably high, you know, above the cut point, not what I would consider a borderline based on what some have suggested would be a good borderline zone, and his response to this was, "Well it's boosting because you did a tuberculin skin test in me." So my question for all of you is what would you do now? Your options are repeat the QuantiFERON, you could do a T-SPOT, treat him for LTBI. I should have given you an option D, which was give up, he's a college student, he's not going to do anything you tell him anyway. That might have been the most popular choice.

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Bob, while we're waiting, it's always interesting. You said something about your schools, you know, your colleges requiring TB testing, and that's always an issue. You know, in Florida actually, we switched more towards TB screening and screening for risk, meaning that we screen for risk, you know, if they have any risk factors for the possibility of TB infection, and then only test those that, you know, have a higher than, you know, would be expected risk. And I think sometimes we forget the difference between screening for risk and testing, and I think we sometimes confuse that screening and testing are equal, and especially when we have a situation like this where none of our tests are really perfect. We can make these tests better by screening for risk. Do you agree or how do you feel about that?

Yeah, I agree. I think it's an excellent point. I'm glad you brought it up. And that is what the schools do. When we have gone to them and had conversations about this, you know, one of the concerns has always been well we can't just target just, say, our foreign-born students. And we have been very clear to saying, No, no, we're not asking you to target your foreign-born students. We're asking you to do a risk assessment," and if you've got a student who is U.S. born and never traveled outside of the U.S. to a high-burden country or had some known exposure, you're done. You don't need to do anything else. That's your screen. If, however, they're from India or from a country with a higher rate of TB, then you should go on to do more. So I think we've taken the exact approach you described.

I agree. And just real quickly, because it always makes me laugh, we get the same thing, aren't we, you know, targeting certain -- aren't we being somewhat discriminatory? And I would explain, we do the same thing for other things. Like we don't screen women for prostate -- we don't test women for prostate cancer, we screen them. And if they're a woman, we don't test them, and it's the same situation.

Right.

But anyway, to get back to question here, 92% of the participants are saying they would treat for LTBI, and 6% are saying they would repeat the QuantiFERON, and about 2% are saying that they would do the T-SPOT. So, Bob, what do you think?

Well, so let's talk a little bit about boosting first, and then I'll tell you what happened. And so this issue of boosting, so does a skin test boost an IGRA? They looked at this in a study in South Africa, where they took 26 healthy volunteers, and you can see they did IGRAs on them. They did QuantiFERON Gold In-Tube and T-SPOT and they did it for four visits prior to the skin test, then placed the skin test and did it for four visits afterwards. And they actually found, you know, a statistically significant change in the IGRA results. They found that it was most pronounced in those that had a positive test. So if you had a positive test at baseline, you were more likely to boost overall. They that had three patients that actually changed from being negative to being positive after the skin test. All three of those patients were, in fact, skin test positive.

Another study that looked at this was in health-care workers, 102 health-care workers in Italy, and the graph just shows stratified by skin test negative by skin test positive. And, again, there was some boosting that was observed, although it certainly wasn't uniform. It wasn't uniform across the skin test positives, or, you know, there were two patients who were negative that boosted above. So, you know, and we've had some experience in a TB Epi Consortium study in health-care workers where we looked at this and drew blood, placed a skin test, and then redrew the IGRAs two weeks later, and we did see some effect. It was more pronounced, again, in people who had positive test.

And I think what we don't know is boosting a good thing? I think it's -- the connotation when people say boosting is -- that it's creating false positives, I'm not convinced that boosting isn't just similar to what we think of with a skin test. It's identifying remote infection in some people, and so they were remotely infected and their immune system hadn't seen those antigens circulating for years or decades, and then you expose them and then retest them, you get a change in their reaction. So it can occur. It doesn't

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appear to be, I think, a major barrier to the approach that, again, some countries have taken, which is skin test is their primary test, followed by an IGRA as a confirmatory test.

So what happened in this case was -- so the student with the 11-millimeter skin test and the positive QuantiFERON, the student health center that was seeing him said -- I'm not entirely sure why, but they said, we want to really treat you for latent TB because we think you're going to take that even though his behavior wasn't really consistent. So they repeated the QuantiFERON, and this time it was negative at a TB antigen minus nil of 0.34. So one-one-hundredths below the cutoff, and his response was, "Finally we agree, I'm negative for TB," and, of course, he didn't take treatment.

So my response to them was, really, I would stop at the QuantiFERON and say, "Listen, you're from a country that's got a lot of TB, you've got two tests that say you have TB, we recommend you take treatment for TB, and if you're not interested, then here are the symptoms for active tuberculosis, and, certainly, we want you to come back. But think about taking latent TB treatment." I've rarely, if ever, found it helpful in these circumstances to try and do a third test overall. And that's different than -- and we'll get to where I do think repeating the test can be useful.

So the next case for you all is a 35-year-old male, HIV infected. He has a CB4 count of 350 on antiretroviral therapy. U.S. born, lived in Denver, never traveled outside the U.S., and didn't have any history of ever being homeless or ever being incarcerated. So no identified risk for TB exposure, and his QuantiFERON was positive with a TB antigen minus nil of 0.85. And the question is what would you do? Your options are treat him for latent TB if the chest X-ray is normal, repeat the QuantiFERON, or do a different test, either a skin test or a T-SPOT as a confirmation of the QFT.

This is a really tough situation here Bob, because you have a very high-risk individual, and luckily his CD4 count is not being that low, you know, not as low, obviously.

Right.

And obviously, you know it looks like a positive, so touch, touch situation here. So it looks like right now about, you know, about 93%, 92% are saying that they would treat for LTBI if the X-ray is negative, and 7% would repeat the QuantiFERON, and about 1.5% would do a confirmatory skin test or T-SPOT. So kind of strong for treating here, I guess.

Strongly in favor.

I guess a lot of people's perception of the risk from immunosuppression.

Yeah. Well, so let me show you a little bit of data, and I'll tell you what we actually did. So HIV-infected populations, obviously, is a very important group to screen for latent TB and treat for prevention purposes. In this study out of Europe, they enrolled 830 consecutive HIV-infected patients, tested them with QuantiFERON. I've always found this interesting, and I would love to ask, if I ever met the author, is all of the people who were positive declined LTBI treatment, which makes me wonder how they offered it exactly. But in their results, from a bi-varied analysis, they found something that's been shown many times, indeterminate results are more common in people with low CD4 counts, so typically related to having a low mitogen, so they just can't respond. Their immune system doesn't respond to the antigen stimulant. Positive QuantiFERONs in this cohort was associated with black ethnicity, birth in Africa, and birth in a country with a high burden of TB. Now obviously those are not independent risk factors. There's a lot of overlap in terms of those risks.

When they looked at their cases of active tuberculosis, they actually had, out of that group, eight cases of active tuberculosis at baseline. You can see the QuantiFERON in this case identified seven out of the eight, so a similar percent to what we saw in the other larger studies of active TB, so good but not great.

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We'll still miss some. And then they followed the patients that were positive and didn't take LTBI treatment, and you can see they found cases among those patients who didn't have active TB at baseline, had the positive QuantiFERON, and didn't take LTBI treatment. They didn't find any cases in the negative.

Now there are some limitations to the study, not the least of which is the negatives didn't get followed up with as intense of follow up as the people who were negative, so it's possible that there could have been cases that were missed among those, but at least, again, some suggestion that the QuantiFERON performs reasonably well, and in HIV-infected population in terms of predicting risk.

Now in a different population a cross-sectional study done at two clinics in Atlanta, they took 336 HIV-infected patients and they did all three tests on them; skin test, T-SPOT, and QuantiFERON Gold, and what they found is that if you took any test positive, they actually -- 8% of their population, 27 patients, had a positive test, but there was only one patient who actually tested positive by all three, and then you can see a mix of people that were testing positive by TST or QFT or T-SPOT. And the conclusion really was that there was really poor concordance among these tests.

Now a little bit about our own experience here, and this is, I guess, where the webinar turns to a bit of a confessional. I have to say that in our own HIV clinic, where TB screening has been part of the policy, you know, since its inception, I did a review when I was doing my infectious disease fellowship, in early 2000, looking at how well we did at getting a result and actually completing a TB screen. And the answer was less than 50% of the people who needed it; meaning they had never been screened before, didn't have a history of treatment for TB, less than half of them were getting a skin test completed. It was because of the challenges around documentation of skin tests, I couldn't really sort out is that really because patients declined to come back in two to three days, when it was offered to them, or were providers not offering it, but we weren't the doing a very good job.

And so in 2009, which was when QuantiFERON really became available to us, we switched. So we replaced the skin test with QuantiFERON in our HIV clinic. And our LTBI testing improved immediately, as you might imagine. These are not patients who are skipping blood draws. Almost all of our HIV patients, you know, on their first visit are going to have their blood drawn, and so adding QuantiFERON into the tubes is not a big deal. What we observed, though, is we found a higher than expected rate of positive tests among our U.S. born HIV-infected population that didn't have any other risks for TB exposure, and so we instituted a policy to say, you know, we want to repeat these QuantiFERONS before we offer them treatment and see how stable they are. You know, there's risk associated with LTBI treatment and drug interaction, we wanted to know if this was real. And we felt that if a person was really infected their QuantiFERON results should be stable.

And so what did we find? And this was a fellow that was working with me, Jake Gray, and he published this in CID, and reviewed, actually at our clinic at Denver Health, and then also at the University of Colorado we had been talking with them. They had instituted a similar policy, and he reviewed the records. So you can see, he reviewed results for over 1300 patients. About 7% of the population overall had a positive test, and just under half of those had really no identified risk for TB exposure and had a repeat test done. And you can see 33 out of those 41 on repeat tests actually had a negative result. So 80% of those folks, arguably, are not infected with TB, and so we've continued that practice today; that if a person has no identified risk -- so this isn't in foreign born person.

This isn't our HIV-infected homeless patient or person that's had a significant history of incarceration. In those groups a positive test we say there's epidemiologic risk and the positive test get an X-ray and treat. But in our patients that don't have any identified risk, we repeat the QuantiFERON first. We don't even get an X-ray until we have a second QuantiFERON that confirms positive. Now, again, assuming they're

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asymptomatic and all of our patients, for the most part, have a baseline X-ray, so we have an X-ray on them sometime in the recent past.

When this was looked at in the meta analysis, and I know I'm showing a lot of meta analyses, I do want to make the point that meta analyses are only as limited by the fact that they're only as the data going into them, and when the published data from smaller studies is very mixed with very different methods and techniques, then the information that you get out of that from doing a meta analysis is going to be significantly limited. But in this analysis, looking at QuantiFERON and T-SPOT, 37 studies, 23 of them actually had concurrent TST done in over 5,000 patients. The end result was that there was moderate predictability and suboptimal sensitivity for all of the tests, and there was relatively similar performance between the TST and the IGRAs.

So what did we do with our patient with a reasonable CD4 count and the positive QuantiFERON? We repeated it. And on repeat test, his QuantiFERON was negative. And, again, in this case not one that I would consider borderline, and so we didn't recommend treatment and didn't, in fact, do an X-ray.

So what about other immune diseases, so we are kind of lumped as an immune-mediated inflammatory disorder, so this is rheumatoid arthritis and lupus and Crohn's disease and all the diseases that are now being treated with biologic therapy, like TNF alpha inhibitors that increase the risk for TB reactivation. Literature review published in the Current Opinions of Rheumatology in 2011, especially found that there was no evidence that the IGRAs were better than the TST. Importantly, and I think what hopefully is coming through in all of this, is that we don't have any test, IGRAs or TST, that are good enough that they can be performed in a vacuum. All of them need to be done and considered in the context of the clinical and epidemiologic risk. And so the kind of expert opinion, if you will, of the authors from the study said that, you know, if you really have a high clinical suspicion -- an example might be a foreign-born person with no prior contact, in that setting you might consider doing both skin test and an IGRA and treating if either test is positive. So not any good data to support that, but it is a recommendation that some have made, again, based on high risk for reactivation if you've got a high epidemiologic risk as well.

Just a couple other studies to show you: So a study looking at QuantiFERON in rheumatoid arthritis patients. These were patients largely BCG vaccinated, and, as expected, the skin didn't perform as well in the BCG vaccinated group. QuantiFERON, comparing rheumatoid arthritis patients to healthy controls, they had a similar rate of positivity, and the inference was that that shows that it performed similar in these patients who are immune suppressed. In dialysis patients, again, the IGRAs correlate better with exposure when you're talking about a BCG vaccinated group.

So the next case for you all to consider, this was a 25-year-old female. She was pregnant, 10 weeks pregnant at the time, HIV negative, born in Mexico and had BCG as a child, and she had a skin test done, and it was 12 millimeter, and she's asymptomatic. The question for you is what would you do? Your options are an IGRA, a chest X-ray, both, or neither?

Bob, again, another scenario, which is something that I think all of us in TB view quite a bit, is really, once again, the whole concept of screening certain populations, in this particular case, individuals who are pregnant. And obviously there's a lot of risk with this in the sense of, you know, you try not to X-ray those you don't, so that result is so important. And, again, the risk factors associated with the possibility of being infected really plays in strongly.

It looks like right now about 75% of the people are saying that in this situation they would go to an IGRA, and, again, I guess because of the history of the BCG as a child. 11% are saying they would go right to the X-ray, and 9% are saying they would go both. And most importantly, and this is really cool, is they are saying -- a large percentage of people are really into this lecture, Bob. You're hitting a nerve, and I think

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it's really working. And I think obviously it's something that is near and dear to all of our hearts. So what do you think?

Great, yeah. No, I'm glad that people are staying awake for it. It's always hard to tell when you're on a phone hundreds of miles away. So it's a little bit of a trick question. We'll get to what we would do in just a second. It's a little bit of a trick though, I'll say, because at ten weeks pregnant the patient was still in the first trimester and is asymptomatic, so a chest X-ray, you might do it but you wouldn't do it right away. And so recommendations for pregnant women are to wait until after the first trimester if they have no symptoms and HIV negative. So in this case I wouldn't do a chest X-ray or both, certainly not right away.

But what about the IGRAs and pregnancy, how well do they perform? So a study published in Obstetrics and Gynecology 2012 took 140 pregnant patients, mean age was 18-and-a-half years. They found nine indeterminate, so a little higher than what we see in, you know, other populations, where I mentioned about 1 to 2% is kind of the expected acceptable rate of indeterminate results, so a little bit higher in this population. They found 28, or 20% that were skin test positive, and 15, or 11% that were QuantiFERON positive.

There was no difference by trimester, so it didn't appear -- and they actually showed the values among the positive patients by trimester, and they didn't differ. Having a positive QuantiFERON did correlate with increased risk of exposure and did correlate with an increased size of the tuberculin skin test. And I included the table in there so you can sort of see what their risk categories were. So they separated by, you know, minimal, low to moderate, and high risk, and then further stratified by history of vaccination and tuberculin skin test positive.

In this case you can see that among the low to moderate risk group, there were 91 with negative skin tests and three of those actually had positive QuantiFERON test. Of those that had low to moderate risk and a positive skin test, only a third of them had a positive interferon gamma, and then the high risk, so known contact with TB, two of them with positive skin test, and both of those, a hundred percent, actually had a positive QuantiFERON.

And so in this case, what we would do is we would do an IGRA, and we would only do a chest X-ray if it was positive. We switched to a policy of doing that sometime around 2009/2010 with our OB/GYN colleagues. And then subsequently, based on our experience, our OB clinics began doing the QuantiFERON themselves, so skipping the skin test altogether. Again, this is a population that gets blood drawn during their visits periodically, and so they began doing QuantiFERONS and now only refer patients to us who have a positive result.

The next case is a 48-year-old U.S. born nurse, no travel risks, prior skin test, multiple prior skin tests, always negative. Gets a T-SPOT and it's positive at 11 spots. Has a chest X-ray that's normal. And the question is what would you do now? So recommend latent TB treatment, check a skin test, check the QuantiFERON, repeat a T-SPOT? What would you do?

So, Bob, again, I think this is one of those dilemmas where we have a group of those individuals where it's generally recommended that you would be testing them despite their risk. I mean, granted, she is a nurse, but with the decline of TB that we're seeing in the United States, health-care workers while they still have a slightly increased risk over the general population, it's not what it once was. So, in general, you know, with no other risk factors, it makes this a little bit more difficult to interpret.

Yeah. And I think we're learning more and more about the performance of these. I'm going to show some information in a second, some data that we were part of collecting and data that has been submitted and will hopefully be published within the next few months. So it looks like most folks voted for recommending LTBI treatment.

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So what do we know about the performance of these tests in health-care workers? And so, again, I mentioned the TB Epi Studies Consortium looked at this, and a fairly large study, four sites; Denver, Houston, Baltimore, and New York City. We had over 2,400 adult health-care workers who were undergoing routine LTBI testing, and we did skin test, QuantiFERON, and T-SPOT in them at baseline, 6, 12, and 18 months.

And really just cutting to the chase on this, baseline tests, the proportion positives were similar. One caveat with that, we specifically tried to target people who were known skin test positive. Because when we started this out, based on the published specificities for QuantiFERON and T-SPOT, we were expecting very low rates of positive results, and so we wanted to try and make sure we got enough people with infection in our group. So we did target known skin test positive people. So including those folks in this, the rate of baseline positive tests were similar.

When we look at conversion, and so this is people who had a negative test at baseline who subsequently had a positive test at some other point in time, we saw conversions in 21 or .9% of our skin test patients, 138 with QuantiFERON, and 177 T-SPOT, or 8.3%. Reversions, and so reversion in this case, I'm saying is people who converted and then had a subsequent test without taking any LTBI treatment. We actually had 12 skin test converters who then got retested. 11 of those 12, in a well controlled study with highly trained staff, 11 of them went from being positive to being negative. With the QuantiFERON and with the T-SPOT it was about three quarters on retest without any treatment reverted to negative.

In this longitudinal study over several years, we had no cases of active tuberculosis. So despite having reasonably high numbers of conversions, if we took any individual test or took the sum of all the tests, we didn't have anyone that progressed to active TB, and only 11 of the health-care workers were actually treated for latent TB infection during the course of the study. There have subsequently been a number of other publications that weren't prospective controlled trials that compared the test directly but observational studies of programs that switched to using one of the IGRAs and subsequently found similar things; that they had a higher rate of positive results than they had previously seen with the skin test. And in the examples where they subsequently repeated those tests without doing anything else, oftentimes those were negative, so they weren't confirmable, not dissimilar to what we found in our own HIV population.

So in this 48-year-old U.S.-born nurse with multiple prior negative skin tests and an isolated positive T-SPOT, what I would do is repeat the T-SPOT. And same thing if it had been QuantiFERON, I would repeat the test before recommending latent TB therapy.

The next case is a 24-year-old student, U.S. born, past history of actually having a benign brain tumor and a seizure disorder. Medications are Oxcarbazepine, folic acid, and oral contraception. She had a baseline skin test that was 15 millimeters and then had a QuantiFERON Gold In-Tube that was negative through the occupational health clinic at the school where she was going. So she was going to school as a pharmacy student. One year later, the occupational health repeated her QuantiFERON, and this time it was positive. Did a chest X-ray, and it was normal. So she had no symptoms, so they referred her to me in the TB Clinic to evaluate her for latent TB therapy.

And my question, is what would you do in this scenario? So a person with increased risk of toxicity based on seizure disorders, a positive skin test, and now a conversion on a QuantiFERON, would you redo the skin test, repeat the QuantiFERON, treat for latent TB? I didn't put -- we could have done T-SPOT, I guess, would have been another option potentially.

Bob, you know, just out of interest, in Denver, who is paying for your T-SPOTs and your IGRAs?

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Yeah, so the ones that we do in our clinic, we pay for. We have, over the past 12 months, worked with our some of our hospital colleagues and others, and we are now billing Medicaid for QuantiFERONs in our Medicaid population and working towards expanding our ability to bill for laboratory tests in patients where there's a payer source.

Definitely very, very important. So right now it looks like we have about 62% of people saying that they would repeat the QuantiFERON in this case. About 36% saying that they would just go on and treat for LTBI, and about 2% that are saying they would repeat a skin test.

Yeah. So this is actually a very recent case, and so I've got a phone call out to her neurologist right now, I'm waiting to hear back from. It turned out that the Oxcarbazepine is not affected by Erythromycins, which I was, frankly, a little bit surprised by, but pleasantly so. So if we wanted to treat her for latent TB infection we could give Rifampin or, potentially, Rifapentine, and we would only need to worry about the oral contraceptive.

The INH, the concern for me is always, in someone with a seizure disorder, lowering their seizure threshold and so I'm looking to get a little bit more information. But I'll tell you what else we did here in a second, and we'll come back to the case. And I put this in here to try and illustrate and be able to talk a little bit about what is the predictability for future TB; meaning, if you have a positive IGRA, what, in fact, is that person's risk of developing active tuberculosis in the future if they're not treated? We have a reasonable sense for what that is with the skin test based on, you know, very large studies done many years ago, where patients were tested and not treated and followed, or declined treatment and were followed, you know, we have a reasonable sense, and I think the most quoted proportion is typically, if you've got a positive skin test and you're affected you've got a 10% risk, lifetime risk of reactivation, and about 5% of that, roughly, within the first couple years after infection.

We don't know particularly well for the IGRA. There are some published studies but they're all fairly limited. This was one evaluation where they looked at it, and found that the incidence of tuberculosis in patients who are IGRA positive was somewhere between 4 and 48 per 1,000, and the incident rate ratio, so the you take what's the -- if you had a positive test versus a negative test, what was your risk? What was the change in risk in terms of progression? And if you had a positive IGRA compared to those who had negative, your risk was about twice, and the skin test it was a little bit less, but fairly similar overall.

When this was looked at in sort of an analysis of both commercial and in-house assays, and then subsequently limited to the commercial assays, again, the positive predictive value was fairly similar, a little higher for the IGRAs maybe than for the skin test. If the analysis was limited to patients, really, that had a high risk for tuberculosis, so coming from countries that had higher burden of TB, the predictability was better.

Importantly, the negative predictive value has been quite high, so being negative on either of these test, having a negative skin test or a negative IGRA, means you have a very low risk of, in fact, progressing to active TB, at least in the short term, in the two to four years or so.

So in the case of the student, because of our experience with QuantiFERON and T-SPOT through the health-care worker study, in a person with no identified risk, our policy is we repeat the questions test. So we repeated the QuantiFERON, and I added the values to this slide. So her first QuantiFERON, her value was 1.21. We repeated it, and it was 2.02. And so, you know, we now have three tests that say she's infected, her original skin test and, now, two QuantiFERONs, so we're recommending latent TB treatment. And the key is just coordinating with her neurologist, making sure he's aware and wanting to know more specifically the risks associated with INH, either high-dose INH, once a week with INH

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Rifapentine, daily INH, which I probably wouldn't do the nine month or four months of Rifampin, which may, in fact, turn out to be the safest option overall.

So shifting gears a little bit, I wanted to talk about high-risk populations in contacts to active TB. I included an older study just because it still amazes me that they were able to pull this off in the way that they did. And I'm not sure anyone outside of the Dutch could do it. But this was the case, and one I'm sure many of you are familiar with, they diagnosed a patient with cavitary smear positive pulmonary TB who worked at a supermarket and had been sick for about a year. And they started the initial contact investigation with household and close friends and family and coworkers, and then expanded. And sort of with each initial expansion, they found higher rates of positive tests than would be expected in the background population, suggesting transmission, and so they decided that they had to test everybody who shopped at this supermarket. I'm pretty sure my staff would revolt if we tried to do that here. If we put up signs at the supermarket that said "Show up for a test," I'm sure how we would pull that off.

But they did greater than 15,000 skin tests on two separate dates, and within this, they embedded a study looking at the QuantiFERON and the T-SPOT. And they used, again, a surrogate marker of risk that included how often the people shopped at the supermarket and how much time they spent at the supermarket when they were there, and then they also collected information, obviously on age and BCG and other things.

And so what they found was the skin test -- having a positive skin test correlated with being older but did not correlate with anything related to exposure in the supermarket. The QuantiFERON and the T-SPOT actually did correlate with their surrogate marker of exposure. And their conclusions from that was that the skin test may, in fact, may be identifying more remote infection, but the QuantiFERON and the T-SPOT they felt was maybe more accurately identifying a recent infection.

One of the other things that they looked at and has been looked at by many, many people in many, many studies is, well what if you adjust the cut point? What if we change the cut point higher or lower, you know, can we improve these tests? Do we think we can get a more accurate test if we do something other than .35, or something other than, you know, the eight spots for T-SPOTs? And the short answer among all of these is that the individual studies they can get better agreement with the skin test or with whatever surrogate marker they're using, but none of these have held up when they have been applied to other groups. And so, so far -- and it's not for lack of trying -- no one has been able to really identify a cut point that is consistently better and would improve these tests without having to repeat them essentially.

Our own experience with this, we've had some huge contact investigations. Again, I'm not sure how we do 15,000 in a couple of days, but we did have a high school student diagnosed with pulmonary TB just about a year-and-a-half ago and we started our contact investigation, and we were using QuantiFERONs because a single visit, and we could get results, and we started with close contacts. We began with those that had two or more classes with the student and found about 53% of those were infected. So we went to anyone who had at least one class, students or teachers, who had one class with the patient, and about a third of those were infected, and so we expanded our investigation to the whole school, so eventually 1,200 students and about 120 faculty that we needed to test.

And this gets to the operational challenges of IGRAs and one of the things I wanted to bring up and mention as part of the objectives. And this is something that may not be true for all labs. I think, actually, the Health Department of San Francisco has a slightly different arrangement to where they don't need to pre-register patients. So for us to do a lab test, to do a QuantiFERON in our lab, we've got to have a patient label, and to do that we've got to generate the label ahead of time. And so we need to know who we're going to test, and we need to know at least enough basic information about them, their date of birth, obviously their first and their last name, if possible, some other identifying information, social security

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number, to make sure that with they're not already registered in the system so we're not creating a new individual who is already part of our system.

The blood draw requires more time than a skin test, so, you know, a well trained outreach worker or nurse can place skin tests quite quickly. It takes much more time to actually draw blood. When you're drawing blood you're much more likely to have patients get lightheaded or even pass out than you do with the skin test. It's very rare with the skin test. It's rare but it occurs, and especially if you're testing a large group, like 1,200 students, you're going to have some that do get lightheaded or even have syncope. There are time constraints, so you've got to -- you know, you can't just deliver the huge number of blood tubes to the lab whenever you want. You're going to have to work with the lab and make sure that there are able to accept those, which is probably going to mean it needs to be during normal business hours. Most labs, you know, in the evenings are operating on a smaller staff and wouldn't be able to handle a huge volume of specimens.

We actually found, you know, our lab had a max capacity per week in terms of tests they could run, and so, you know, we weren't just doing this contact investigation, we were doing our screening of immigrants and refugees and other high-risk groups, and so that was going to be a barrier, and then there's the increase costs for testing the worried well. So anyone who has done large contact investigations or even small contact investigations will have had the experience where people will show up to get tested, when you start asking them the questions, it turns out they're not a high-priority contact.

Now with the skin test it's usually not a big deal, and they're there and they're worried and you place a skin test on them. When you're talking about drawing their blood and doing a test, if you haven't preregistered and you don't have their name, you may not be able to do it. And, you know, it costs more to draw the blood and run an IGRA than it does to take a syringe and put a skin test on the person, and so all of those things really need to be considered.

And so what we ended up doing for our investigation, because we determined that with QuantiFERON alone, we were not going to be able to test these students in what we would consider a timely way, and we wanted to get them diagnosed and we wanted to get them on treatment so that we could, ideally, finish therapy before they get out of school and did what teenagers do and high school students do, which is, you know, disappear, and our adherence was likely to be low after we lost track.

So we came up with a plan where we continued to use QuantiFERON for anyone who was foreign born or BCG vaccinated. And there are some U.S. born students who, you know, born in the U.S. but then maybe lived in another country and got BCG. So anyone with that sort of history got QuantiFERON. And we did skin tests for everyone else. And with that approach, we were able to get, really, the majority of those 1,200 tested in less than a month, so in a very timely way.

And so the logistical consideration sometimes become as important as -- or even more important than which tests you really like, and you have to be prepared if you're going to -- especially if you're going to go in and do a big group with QuantiFERON, it's very different than testing a big group with the skin test.

Just one slide on costs, but, again, I did want to mention costs. I guess I have a couple slide. One published reference on cost, and this was one published in the "American Journal of Respiratory and Critical Care Medicine." They used a Markov Model to estimate the cost screening using a skin test versus IGRA in different risk groups. And essentially what they found was that the IGRAs were more cost effective than this skin test when the LTBI was prioritized towards close contact, HIV infected, and foreign-born persons regardless of the time in the U.S.

Now cost is a funny thing, because the cost of something, really, it comes down to who's paying for it and what are they actually paying for. So in the case of IGRAs and in the case of the skin test, the costs in

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many of these models and the costs considered, there's the laboratory costs versus the supply costs of the skin test. Those are very different, and a skin test is much cheaper. If you factor in the person time and two visits, then the skin test becomes more expensive, but those are sort of what I would consider soft costs that aren't really tangible to, say, a hospital or even to a TV program. If you've got the people, yes, in theory, they could be doing other things or, you know, the lost time to patients for two visits of the skin test has some societal costs, but those are costs that aren't borne by a TB control program for example. And so, you know, it comes down to some real current costs versus the potential future costs. And some of those potential future costs do fall into the category of cost avoidance. So if you're doing skin tests on BCG vaccinated patients and doing a lot of X-rays and doing a lot of LTBI treatment that I would say is unnecessary, because of the affects of BCG, then those really -- the cost avoidance for that, in my mind, really does favor the IGRAs.

So just to wrap up and kind of coming back to those objectives from the beginning, we'll talk about the benefits of using the IGRAs in different populations at risk for TB, you know, I think they really are maybe slightly better for detecting active tuberculosis, although, again, still not good enough to be a test to rule it out. They're definitely more specific in BCG-vaccinated patients, and as I mentioned before, this is a large population of the highest risk patients in the U.S. I think they're comparable or maybe slightly better in HIV patients and other immunosuppressed patients. I think it could also be argued that the fact that the test tells you when it fails is maybe of some value and so you know that you need to repeat it later, whereas the skin test that fails looks just like a negative, so that ability to know when the test fails has some value.

Challenges, it's not sensitive enough for active TB. So far there's only a modest ability to predict future TB cases during short-term follow up. This is where the data is very limited, but, you know, at least thus far, doesn't appear to be a quantum leap forward relative to the skin test. And as many people have said before, most of us don't necessarily care who's infected with TB, we care who is going to get active TB, and if we could identify those people better, and avoid treating people who really aren't ever going to progress, then our prevention efforts would be much more cost efficient.

And another limitation or challenge is that I think we've now learned that there are higher rates of false positive tests in lower risk populations than what was originally reported. The early reports on specificity for these tests that showed 98/99% specific were generally done in higher-risk populations. And when we have applied these in U.S. health-care workers, in our U.S. born HIV-infected populations, we found, in fact, that the specificity is probably lower and may be closer to 96%, and so you get a 4% or so rate of false positive results, and that's important to keep in mind.

Operational advantages, it's a single visit. It's less subjective. You can't under value, again, the importance of being able to find the results. It does make analyzing epidemiologic data much more easy, which is the reason we have hundreds and hundreds of published studies and dozens of meta analyses, and so there are very real operational advantages. There are disadvantages. So they need to register patients in the lab, the limitations for the lab, the risk of syncope, and the time required to draw blood, and then making sure someone needs to then go back and go into usually an electronic record and look up the result, as opposed to the reading a skin test, calling it negative, and giving someone a clearance card is another example.

The cost implications, you know, it's often broken down into the lab costs versus the time lost associated with the skin test, and that comes down, typically, to who pays. So who is paying for the testing and who is paying for the follow up, and, really, what is the risk in the population being tested. And so my recommendations, I think, first and foremost, we need to test people who have risk for infection, and so these are primarily people born or lived in high-burden countries. I think we should focus -- within that group, we should focus on those with risk for exposure and risk for progression, so foreign born, HIV, diabetes, end-stage renal disease, all the other risk factors for progression of the disease.

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I think, overall, I prefer the IGRAs where they're available. They're better in BCG vaccinated people, and these are the group, the foreign-born persons living in the U.S. are the highest risk for future cases, and so I think if you had to pick a test, I would pick the IGRAs and I would apply it in that group. And, again, as I've mentioned several times now, I think, being able to retrieve the results easily now and in the future. If I do attest now I'll be able to find it in five or ten years, I think that has value.

I do recommend repeating all positive IGRAs in lower-risk people, and I include U.S. born homeless, in Denver certainly, as a lower population. We repeat the IGRA before treatment now. I will say the caveat is if we have a person that we're not going to offer treatment to or they say, "I would never take treatment," we don't waste our time repeating the IGRA at that point. But if it's someone we would treat and they're interested in treatment, before we start, we repeat the test. Same is true with health-care workers. U.S. born health-care workers with no foreign travel and no known exposure to active cases, we repeat the test.

And we do, and I would recommend, or at least recommend people at least consider is repeating an unexpected positive result in populations that have risk for progression but, really, no risk for exposure. So you're talking about someone with diabetes or someone with HIV, they've got risk for progression, but if they're U.S. born and no real contact for risk, I would repeat the test before offering therapy. And I'll stop there.

Bob, I know you can't hear all the applause due to our limited technology, but I promise you it's all throughout. That was fantastic. Thank you so, so much.

You're too kind.

Hey, you know, I want to say to everybody that we have gotten a ton of questions, and I really appreciate it, and I'm going to do my best to try to pull them together as much as possible, and please continue writing your questions, and if we don't get them by the end of this session, we'll do our best to get them to Bob and to our other distinguished participants to try to get you answers. With that, if it's okay, I have some questions, Bob.

Yeah.

And I'd like your comments. And I also -- Sundry, are you on? And, Jerry, I know you may -- Jerry, I know was on. I'm not so sure if he's still on. I know he had another commitment.

Dave, I'm on, and I think Jerry is on as well.

Fantastic. Jerry, I think, is on limited, you know, time, so I guess what I want to do is start with a question we're getting a lot of. And, you know, I'm guilty of it, and I know we talked about this wobble effect effect, and, yet, I think we didn't quite define what the wobble effect is and what we're seeing, how what we said is the cutoff points may really be affecting that.

And, Jerry, I know you've written some and I've heard speak on this effect. Do you feel comfortable maybe in answering some of the questions as far as what we're seeing is what is the wobble effect, and especially when it comes to health-care workers that required to get repeated testing, how will we see that being affected? Jerry, are you there?

I think you need to tell him how to unmute.

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I'm sorry. Jerry, the way to unmute, push "*"7." Thank you, Sundry. Okay. Bob, how do you feel? Do you want to try to maybe address that?

Yeah, absolutely. Yeah, I'm happy to talk about it. Yeah, so the wobble effect has been described and defined as people whose results are near the cut point, such that a small change would push them either above or below that cut point. So in the case of QuantiFERON, that .35, and oftentimes a range has been, you know, .2 up to .7, so if you fall in that range, you may be in a kind of a borderline where it wouldn't take much difference in a repeat test to either push you either above or below, and T-SPOT similar.

And there have been a number of studies published showing, that, yeah, if a person's initial test is near the cut point, they're more likely to have a change that pushes them above or below than someone who starts very far away. Someone who has a very negative or a very positive result is less likely to cross over. And so it's been that the theory that has led people to look at, well, should we have a different cut point? Or in the case of, like, the skin test where we actually say, you know, you need to go up by ten millimeters to be considered a conversion, should we have some similar criteria to define a conversion related to a T-SPOT or a QuantiFERON? And there is a lot about it.

I didn't get into it specifically, but the short answer is you can make the test look better depending on what you're trying to look at by altering these cut points. But in the end, particularly in our experience with the low-risk health-care workers, not everybody with what we would consider a false positive conversion converts into this wobble zone or this borderline zone. We see people that start very low, had a very high repeat follow-up test, and on repeat were very low again. And in our example, because we were doing all three tests simultaneously, we could compare their results against the two other tests, and most people who had a conversion, regardless of how strong that conversion was, converted to only one test. So they had converted to only one out of three tests, and their conversion wasn't stable.

And so the wobble is a good theory. It's an interesting theory. I've just, from everything I've seen, I'm not convinced it's something that's going to be practically useful in improving our ability to use these tests in real life.

Bob, I totally agree. I think the key would be that to recognize, and for all of us to recognize that it does exist.

Yeah.

And just like you stated over and over again, where you can interpret these tests in a vacuum, that you've got to take it in conjunction with the clinical picture. So what makes it difficult, I think you'd agree, in health-care workers, especially health-care workers that are working in settings where there is not a significant risk of TB, that when you see these types of results and you see a positive, I guess the first thing to do is to think about is this a possibility and then go forward and try to investigate it further. Would you agree?

I agree. No, I think that is the right approach.

I think that Jerry might be able to speak now. Jerry, are you on?

You know, those CDC equipment, you know, that's what the problem is.

Yeah, that's the problem.

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Look, Jerry, do us a favor, when you can speak, just cut right in. We'd appreciate it. We'd really like to hear your perspective. You know, Bob and Sundari, I wonder how you feel. But I think one of the biggest issues I hear, and, you know, a lot of the questions, you know, I'm seeing is a lot of questions going why was the TST negative one, why is the QuantiFERON positive in this patient. And I think one of the big mistakes I personally believe in this whole field is that we use terms that are actually not true at all. Like we're constantly using things like the sensitivity of this test is this, and the specificity of this test is this. But in order to determine sensitivity and specificity, you need to know what the true positive is or the false negative.

In reality, we do not have a gold standard. So one of the big problems is we truly do not know who is infected, just like you said, Bob, and how this test was developed. It was developed for cattle. And interestingly enough, in cattle, they truly do have a gold standard, which is that they take the cattle, they grind them up, and then they look for TB, and they actually knew who was infected. In humans it's really hard. I know you serve on the TBESC and the TBTC, and I know we've been trying to put that through the Ethics Committee. It's very hard to get our patients to grind themselves up.

So I was wondering, you know, to explain some of that frustration, Sundari, and maybe, just, you know, the idea that we really just don't know who is infected and that's why we have to utilize something like Bayes Theorem, where these tests become more -- they have a better ability to predict, your know, a result if you use it in a high-risk population, Sundari. Do you agree, or how do you feel about that?

Yeah, absolutely. And I think these cases have been excellent and demonstrating just what you're saying, Dave. So you can see, and some of the studies that Bob showed as well, that targeting high-risk persons for testing, I think, is one of the keys. And then, as we saw from the cases presented, in some circumstances you may wish to use both tests if you want to increase your predictive value. Again, the lack of a real gold standard is an issue, and that is why that in very complicated cases it may even be worth seeking some extra consultation when you're not sure how to interpret these different tests.

And I think another point is -- Bob, I think you made this point -- when you have a contact to a smear positive pulmonary TB case, that's when I think you really want to optimize your ability to detect LTBI and treat prior to progression of disease, and that's a situation which you want to try to fully -- I personally would use, if either test were positive in a situation like that, I think I would treat that person for LTBI. I don't know what you think about that.

Yeah, our approach is to use one or the other. We don't use both in contacts. But if we use the skin test, then I would generally say, if we've chosen to use the skin test, we make our decisions based on the skin test and don't subsequently say, "Well now I'm going to do an IGRA to confirm it." We don't really typically take that approach.

And in children younger than five do you routinely use just TSTs or are you also -- are you using IGRA in that population?

No, we're using IGRAs in that population, down to the age of two.

Yeah, I think that's a situation in which, in some instances, we've used both tests in order to optimize potential for detecting LTBI.

You know, one of the things -- you know, while we're picking on health-care workers for a second, you know, one of the questions I have is, like, for a health-care worker who requires annual TB testing, if the skin test is positive and the subsequent IGRA is negative, how do you recommend screening them each year? You know, Bob, you want to try to address that and your comments?

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I think, you know, one of the other issues that's being discussed in this is that a lot of facilities are changing the way they're testing. They're going from skin testing to IGRAs, you know. And some of the questions, again, on that same thing is is there any set recommendation, is anybody recommending tests all health-care workers with IGRAs or all health-care workers with skin tests? So, and there was two parts, which is, one, you know, is there any set guidelines with how to test health-care workers; and, effectively, what do you do with somebody who has a positive skin test before and now they're being tested by IGRAs?

So there are guidelines for testing health-care workers, although they don't differentiate, you know, TST versus IGRAs. You know, it's here's who should be screened based on risk. My own bias is that when you look at it, when you look at the epidemiology of TB in the U.S., and you look at health-care workers overall, I think that increasingly that's not a significant risk for TB exposure and infections. And what we're really talking about is not the known exposure to an active TB patient. You know, the annual screening is looking for the occult exposure to a TB patient that didn't subsequently get diagnosed with TB and led to an infection. The risk and the likelihood of that is increasingly small.

And so I sort of am in favor that we should move more to the model of what we recommend with our universities, is that we should be doing a risk screen every year. And the greatest risk is probably not working in an institution in the U.S., but if people do volunteer working internationally or paid work internationally or, you know, they do vacation and go on missions and things. I mean that's probably a greater risk and people who should be screened. I don't think I should stop being screened. I work in a TB clinic. I have no problem being screened annually. But I think that screening the, you know, receptionist and random people who work in, you know, our OB/GYN clinics and everywhere in our health care doesn't make good sense.

When we get the example of a person who's got a positive skin test and then someone did an IGRA and their IGRA is negative, and they get referred to me, my recommendation generally is if the program at the place you work with uses skin test as their method, then I would treat it as a positive skin test. And what do they normally do, they do symptom screening. I don't recommend they now try to complicate the process by adding in IGRAs for the handful of people that have positive skin test and negative IGRAs, and make a process that I think should probably either be simplified or go away into something more difficult. So that's my recommendation. If your occupational health uses IGRAs, use the IGRAs, and make your decisions based on that, and that's how I counsel folks.

I mean just to make -- and Sundariy, I want to hear. But what makes it even more complex is, as you know, because one of the reasons we test health-care workers is to detect occult infection, as you stated, you know, one of the things is that means that you need a good baseline. So one of the things the becomes very interesting is that many facilities, when they switch from skin testing to IGRA, unlike usual where we only let -- they will test annually those who have the negative previous skin test, now you really need a new baseline. So many facilities are going back and testing everybody with IGRAs in order to get a good baseline, you know, and that's complicating things, and that's at least what many people are recommending.

Can you hear me now?

What I'm getting at is that --

Jerry, can hear you now.

I'm sorry?

I think Jerry is trying to chime in there.

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Oh, sorry, Jerry. Go ahead, please.

I'm glad you can hear me. I just wanted to say that in cities that we've done – where we've gone back and tested the people that were skin test positive and included them for IGRA testing, a substantial number of those are the ones that actually convert and revert back and forth.

I also wanted to comment a little bit on the suggestion that people that are screened annually don't need to be tested every year. And, you know, the guidelines, both at CDC for testing and for health-care workers would support it. If you have health-care workers that are low risk, you know, they don't need to be tested every year. Your chances of having a false positive are greater than a true positive, even with a test such as the skin test or IGRA when the specificity is greater than 99%. If it were 99% and your prevalence was 1%, which in most health-care workers is less than that, your chances of a false positive exceeds your chances of a true positive. And so for those people that are negative in prior testing and have no reported exposure or increased risk, it's reasonable not to test those people repetitively, annually.

Jerry, I totally agree. But, you know, and that's where I think we're going to be seeing soon with the dramatically changing epidemiology of TB in the United States as we're hearing reconsideration of a lot of these, quote, unquote, recommendations. And even if you tested them every other year, you'd still run into these issues. So I appreciate that very much.

Can I make one more comment, and that is in regard to testing. I think one of the advantages that we have with more tests is that we actually can improve our ability to not treat people that don't need it. So if, by chance, in your health-care setting you are screening people and you don't identify any risk and the person has a positive TST or a positive IGRA, repeating the test actually increases the likelihood that you're going to discover that the person doesn't have a true positive and doesn't, then, warrant treatment. And in the vast majority of those people that we've seen there is no evidence in subsequent testing or evaluation that puts them at increased risk of developing TB.

And I think, Jerry, you'd agree, that is going to be the key, is following up these studies long term to see what the outcome is, because as Bob has stated. In reality, we really don't care who's infected, we care who's going to develop TB. And ultimately it's those prospective studies, I think, that will lead a lot of – that will really enhance our knowledge in this case.

Yeah, I think the limited data that was presented by Bob shows that the predictive value for who's going to develop TB is really much greater when a person is at high risk to start off with. So, again, I don't think we can underline that point enough.

And the importance of, as we're saying, screening for risk first, you know.

Exactly. And I saw a question about a risk assessment questionnaire somewhere in there.

Yeah, and, I mean they're generally – I mean, and, again, we can provide to the – I know the CDC, I mean those are out there, the risk assessments. And, you know, when you look at even, you know, the CDC guidelines, there's definitely clearly risk assessments. And we usually follow those, you know, for the same ones we would use for skin testing, we would test, I would think you'd agree, would apply to the IGRA, too.

Yeah.

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Let me – I apologize, just because we're running – we're getting close to time, we've got a lot of questions that came over and over. So one of the big questions we got was timing. You know, Bob, one of the things you stated in your lecture, which we agreed is to repeat the – you know, you have somebody who has a positive skin test, how long should you wait before repeating the IGRA, especially concerning – and, Jerry, I'm very interested in your opinion in this too, but especially given the fact that there may be some boosting, as you just discussed.

Or, you know, Bob, as you stated before, if you have somebody who has a, you know, an indeterminate QuantiFERON, how long do you wait to repeat the QuantiFERON? Or, lastly, let's say you have somebody who has an indeterminate QuantiFERON and you want to do a T-SPOT, is there any set amount of time that you wait before repeating any of those tests? Bob, I'm going to ask you first?

Okay. Yeah, so for the indeterminate, I would say I would wait if there's something identifiable that could get better. So say, for example, the person had a viral illness at the time it was drawn and you had an indeterminate, wait until the viral illness is gone. If someone has a very low CD4 count and you're starting them on antiretrovirals, wait until their immune system has improved, because that's likely the reason you got the indeterminate. If you get it in an otherwise healthy person, I think repeat it whenever it's convenient, and I wouldn't worry about waiting some specific length of time.

Jerry, do you want to comment on that or Sundari?

It sounds reasonable to me. I agree. In general, you know, I have a tendency to repeat it, and the majority of them, even among HIV infected that were indeterminate that end up being, you know, giving us our usable result. And so, you know, sometimes it can help immediately or soon after the first to repeat it. but it does make sense to, if you're limited by funds and things like that, to wait until the reversible condition is improved.

Now, just to go back, you stated, you know, before about, you know, the issue – well, actually, let's go do this first. I apologize. But one of the questions also was being asked about, you know, the statement about children under five. And, you know, what are the recommendations for IGRAs right now, currently, in children under the age of five?

So, from the CDC recommendations it's -- the TST is preferred. It doesn't mean that the IGRAs will not be useful. It's just based on various factors, including the difficulty in which it is – a blood draw is in children less than five, the increased number of indeterminate results, less data that was available is what the recommendations for preferring the tuberculin skin test were based on.

Right. So I think the key is that, you know, if you look at the CDC is preferable, you know, in the Red Book, I think you'd agree for pediatrics is also pretty much the same which is them stating it's preferable. But, again, I think what you're also hearing is that there's new data that is coming out that may, you know, influence those recommendations. Bob, do you agree with that?

Yeah, I agree. I think that's the challenge. And, you know, for understandable reasons it's uncomfortable for people not to treat a child with a positive skin test, negative IGRA. You know, we don't want to be wrong. But, again, if we look at the data in BCG vaccinated, I think it doesn't make epidemiologic sense to think that all those children have latent TB, and, certainly, the rates of active TB we see in those and what we know about BCG in adults all, in my mind, is evidence to suggest the IGRAs in that group are going to be better tests. Now, in non-BCG-vaccinated children it may be different.

I think -- did we just lose Bob?

Nope, I'm still here.

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Oh, okay. No problem. Just – I heard – it may just be my phone.

Do you think we could just introduce those – the PPD questions to folks real quick?

Sure, I think that's a good idea, and that's what we'll do. Again, let me just say, you know, two things real quick. First is that I know we have a bunch of questions, and we'll try to get back to you with the answers. And I really want to thank you for, you know, first, Bob, an outstanding presentation. I'm looking at the chat here, and everybody's saying you did a really amazing job, and I could not agree more. They're already asking for an encore. And I have my lighter out right now, or my cell phone on; that tells my age. But, Bob, just simply unbelievably fantastic, thank you very, very much.

I want to also thank Jerry and I want to thank Sundari for the discussion. And I do think this is something that warrants even more questions. And I think this is changing so rapidly that I wouldn't be surprised if, real soon, we do come back with a part two.

But in the meantime, as you know, the CDC has made an announcement or an advisory, yesterday, you know, that stated that, again, that there was a shortage in the supply of Tubersol, as well as difficulty getting Aplisol, due probably to the Tubersol shortage. And what we've asked here, and the CDC has asked our help, Bob, to answer a couple of questions with the BPD shortage to maybe help define this a little better. So, Sundari, I want to turn it over to you, if that's okay.

Yeah, sure. These questions will be asked in better detail to every one of the 68 funded jurisdictions. But since we have all of you on the line, I thought this would be a great opportunity to just take sort of -- clearly this isn't a randomized survey or anything, but just to poll of all of you out there if you're part of a TB control program just to weigh in to get an idea of how severe the PPD shortage is, who's seeing it; that is, what percentage of those of you on this line today are feeling impact in your public health programs. And we'd like to know not only about Tubersol but Aplisol. And we're asking questions about how the situation is now in comparison -- well, comparison to just a month ago. And then also whether you've been hearing that non-public health sector institutions, academic institutions, VA hospitals, private docs, you know, whether they're reporting this as well. And then, lastly, whether you feel like it would be worthwhile for CDC to put out another notice to readers in MMWR format summarizing what we know to date and what potential recommendations we have.

I will take a screenshot of this, and this will be extremely useful information for us this week as we collect information in a more systematic fashion from all of our funded jurisdictions through our program consultants and the field services and evaluation branch. So I really appreciate Dr. Ashkin, SNTC, allowing me to introduce these questions into this webinar, and thanks for answering them.

Well, Sundari, thank you. And, again, you know, I can't tell you, given the current situation that we're facing, Bob, again, I can't thank you enough for really trying to help in, what I think, is a critical time. So, Bob, first of all, thank you very, very much, again. And I want to thank all of you for joining us today. I want to thank you all for also participating not only in the webinar, but also helping out with that PPD questionnaire. As you guys know, please, you saw the instructions on the screen, please follow them with your e-mail for the evaluation so you can get your CEU and CME credits. And I want to thank you all for joining us.

I want to remind you that we'll be back next month. On September 25th we have another topic, which I think is very, very relevant to all of us in TB, which is TB and diabetes, including challenges in treatment, diagnosis, and management. So, with that, Donna, and my thanks to Donna and Karen and Steve for always backing us up, and other than that, thank you for everything you do. I hope you enjoy the rest of

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your summer. And we'll see you real soon. Thank you very, very much from the Southeast National TB Center. Thanks again.

Great. Thank you.

Thank you for joining today's event. I will leave these questions up for just a few more minutes if people want to continue answering them. Again, we appreciate your time today, and we will be archiving this webinar on our website within the next few weeks. Have a great day.