Verbatim Transcript

2012 HIV Diagnostics Conference Final Feedback Session: Proposed Recommendations for Diagnostic HIV Testing Algorithm
December 14, 2012, Atlanta, Georgia

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Acronyms

Acronyms	Term
Ag/Ab	Antigen / Antibody
APHL	Association of Public Health Laboratories
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CLSI	Clinical and Laboratory Standards Institute
CPT®	Current Procedural Terminology
CROI	Conference on Retroviruses and Opportunistic Infections
DHAP	Division of HIV/AIDS Prevention
DNA	Deoxyribonucleic Acid
ED	Emergency Department
FDA	Food and Drug Administration
HHS	(Department of) Health and Human Services
IA	Immunoassay
IgG	Immunoglobulin G
IgM	Immunoglobulin M
MMWR	*Morbidity and Mortality Weekly Report*
MSM	Men Who Have Sex With Men
NAT	Nucleic Acid Testing
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NIH	National Institutes of Health
NMAC	National Minority AIDS Council
PEP	Post-Exposure Prophylaxis
POC	Point-of-Care
RNA	Ribonucleic Acid
SAMHSA	Substance Abuse and Mental Health Services Administration
STD	Sexually Transmitted Disease
TRUVADA®	Emtricitabine/ Tenofovir Disoproxil Fumarate
UCSF	University of California, San Francisco
UNSAT	Unsatisfactory for Review

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Final Feedback Session:
Proposed Recommendations for Diagnostic HIV Testing Algorithm
December 14, 2012

Session Panelists

Bernard Branson, Michele Owen, and Laura Wesolowski, DHAP, NHHSTP, CDC

Overview

Overview: During this session, staff of the Centers for Disease Control and Prevention solicited verbal feedback from participants of the 2012 HIV Diagnostics Conference about the proposed HIV Diagnostic Testing Algorithm. Feedback was solicited according to procedures of the U.S. Office of Management and Budget to ensure public participation in shaping expert deliberations about documents classified as influential scientific information. (U.S. Office of Management and Budget, Final Information Quality Bulletin for Peer Review, December 16, 2004. Available at: http://www.whitehouse.gov/sites/default/files/omb/assets/omb/memoranda/fy2005/m05-03.pdf

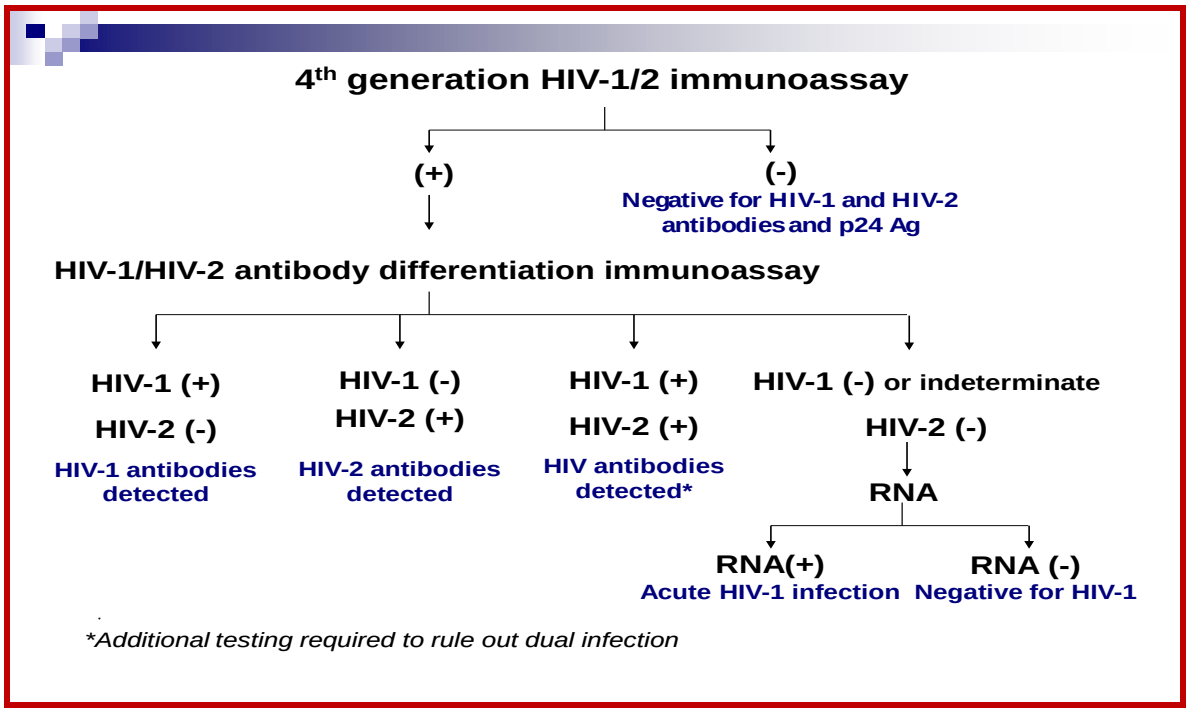

Figure 1: Recommended HIV Diagnostic Testing Algorithm

Draft Recommendations

1. Initiate screening with a 4th generation Ag/Ab combination immunoassay (IA)

2. Reactive (repeatedly reactive) specimens should be tested with a 2nd generation Ab IA that differentiates HIV-1 from HIV-2 antibodies.

3. Persons whose specimens are positive on the initial IA and antibody differentiation IA should be considered positive for HIV-1 or HIV-2 antibodies and initiate medical care that includes laboratory tests such as viral load, CD4, and antiretroviral resistance assays.

4. Specimens reactive on the initial IA and negative on the HIV-1/HIV-2 Ab differentiation IA should be tested for HIV-1 RNA. A reactive result indicates Acute HIV-1 infection.

5. Follow this same testing algorithm (beginning with 4th generation IA) for specimens with a previous reactive rapid HIV test result.

Alternatives

1. If 3rd gen HIV-1/2 IA as initial test: perform subsequent testing specified in the algorithm.

2. If alternative 2nd Ab test is used (e.g., WB or IFA): If negative or indeterminate, perform HIV-1 NAT; if HIV-1 NAT is negative, perform Ab IA for HIV-2

3. HIV-1 NAT as 2nd test: if positive, HIV-1 infection; if negative, perform HIV-1/HIV-2 Ab differentiation assay.

Considerations

1. Supersede
   - Recommendations for Use of Western Blot (1989)
   - Recommendations for HIV-2 Antibody Testing (1992)
   - Protocols for confirmation of reactive rapid tests (2004)

2. Screens for both virologic and serologic markers of HIV infection
   - Incorporates NAT to resolve discordant IA results
   - Identifies acute HIV-1 infection
   - Reduces indeterminate test results

3. All IA-positive specimens tested for HIV-2

4. Emphasizes sensitivity
   - For initial testing
   - During supplemental testing

5. Rare false-positive antibody test results might occur
   - False-positive results would be discovered during subsequent laboratory testing recommended as part of initial clinical evaluation

Feedback

Bernard Branson, CDC, Session Panelist: The recommendation is slightly different than 2010. We are calling to initiate screening with a 4th generation Ag/Ab combination assay. There was some talk about, you know, most sensitive—calling this the "most sensitive" assay, and "sensitive" is very relative in terms of where we're going. So, this is the first recommendation that I'm happy to solicit any comments on.

Robert Coombs, University of Washington: Thanks, Bernie, for again leading us through this journey. A couple of things: I like that fact that the algorithm is flexible. Oh, I'm sorry, Bob Coombs, University of Washington. I have no conflicts, and I started life with a rotary phone. There is flexibility starting with the 3rd generation versus the 4th. At least as I read it, it's an alternative for sites that maybe have lower prevalence of infection. I think in combination with confirmatory tests, such as a Multispot or equivalent, the algorithm performs very well. A point I'd like to bring up is, because obviously cost comes into this as you've alluded to, and Joan, who keeps tabs on the costs of my lab, suggested to me that one of the things to maybe consider is when you make recommendations about changing platforms and approaches, is there any mass purchasing power available for the public health labs that the government could oversee? I'm that could bring prices down for some of these platform changes for people if there was an effort to do it. The other thing that I want to just mention—I don't know if this is the appropriate time, but since you alluded to the signal, the cutoff ratio, I don't have a problem with 1, which is what the manufacturer's have determined from their receiver-operated curves. What I was suggesting was that the gray zone, which is on the lower end, be a consideration in labs, certainly labs that are processing samples from high seroprevalent areas, that there the issue of perhaps looking at some value below 1 to trigger a nucleic acid test might be appropriate. I'm not suggesting that it be changed overall, but that's what we deal with on a real-time basis anyway, and maybe that type of approach, maybe with more data, but I don't know if we need more, could be put in as some sort of caveat on the table to alert people to that fact that that may be a worthwhile endeavor. The other comment I had was with the HIV-2 testing, and it specifically states DNA. My recommendation would be to change that to nucleic acid, with a caveat that a significant portion of HIV-2 infected people may be RNA negative, and

in that case, DNA would be required to exclude the infection. Those are my comments. I thought it was great, and flexible enough, I think.

Bernard Branson, CDC, Session Panelist: Thanks. I'd like to actually just comment on a couple of your comments. One is, I think laboratories have been in the practice in different places of having a gray zone, and I think that is a thing a laboratory chooses to do. I'm not sure that we can issue a recommendation that you "must."

Robert Coombs, University of Washington: No, no, there's no must. The recommendation isn't a must.

Bernard Branson, CDC, Session Panelist: And so I think that it's a good idea to do. Similarly, the idea of—and I appreciate the comment that you talked about with respect to HIV-2 DNA is similar to the package insert indication for the APTIMA® right now, which is that if it's positive you can trust it. If it's negative you can't necessarily, and I think that was the intent behind the DNA recommendation, and we very much appreciate that comment.

Sindy Paul, New Jersey: I don't have any conflicts, but I would like to thank Steve Ethridge and the Planning Committee for a wonderful conference. My comment on starting with the 4th generation is that this is great if you are in a laboratory setting, but for those of us who do a lot of our testing not in a laboratory setting, without access to a laboratory like in the public health settings, I'm hoping that the recommendation will also allow the flexibility until there is a point-of-care (POC) rapid 4th generation test, that we can continue to do, you know, what Dr. Martin presented for New Jersey, a rapid-rapid type of algorithm because the bottom line, as Bernie said, is really getting the result to the patient and getting the patient into care. And all of our data in New Jersey shows that being able to give the patient their results on site and getting them linked into care gets more people into care and retains them in care. So, please allow us to still have that flexibility as the technology and the Food and Drug Administration (FDA) approvals are going through.

Bernard Branson, CDC, Session Panelist: Sindy, I'm really glad that you brought that up and I want to really clarify something, that our intention with this recommendation is making recommendations to laboratories, so we'll have some time to talk about this whole issue, because both Michele and I have been "beaten over the head" with respect to what to do after a rapid test kind of thing. But if there's any confusion, please help us to make sure to clarify that this is a recommendation for what laboratories should do. The whole issue of what everybody should do and where rapid tests fit in is something that I think has to be addressed, but I think it broadens the scope of this recommendation such that if we try to cover that, the Europium would definitely be out before the algorithm comes out.

Sindy Paul, New Jersey: Thank you. You know, it would be great if there is a clarification or a caveat someplace that people realize that this is for laboratory-based as opposed to point-of-care.

Bernard Branson, CDC, Session Panelist: Well, this in particular is for laboratories. This is, I think is our intention. Michele, is that correct?

Michele Owen, CDC, Session Panelist: Yes, absolutely, yes.

Benjamin Tsoi, New York City Program: Conflicts other places, but not for today. I basically echo what Sindy says. A lot of people are still going to be using rapid. In terms of starting with the 4th generation, we've been trying really hard to get a lot of hospitals in New York City to move to a 4th gen. It's been a struggle. I think it's reasonable to recommend 4th gen as the start, but I think a lot of people are still going to stick with the 3rd gen, at least for a while. I mean, the recommendation of using the Multispot is still totally applicable to the 3rd gen.

Bernard Branson, CDC, Session Panelist: So, I think just to be clear, what you are saying is that you do think that we need to make sure to include the alternative, or what to do if you start with the 3rd gen. Great.

Barbara Werner, Massachusetts Department of Public Health: I have no conflicts. I remember rotary phones, and actually, I remember my grandmother had one of those that didn't even have a rotary dial. You picked up something and an operator came on.

Bernard Branson, CDC, Session Panelist: HTLV-III days. Right?

Barbara Werner, Massachusetts Department of Public Health: I will point out to Sindy and others that the title of this is "Diagnostic Laboratory Testing for HIV Infection in the US," so I think you've covered it there, and if people know that some time in the future there'll be something about rapid tests and what to do with those, it's clear in the title to me anyway. With regard to the language on "FDA-approved 4th gen should be used" I don't know if you want to say—I guess "should be" is okay—but whether you want to say "is the preferred initial test" or not, and maybe somehow link it to the back side here that says "alternatives for use" and then you say what to do if you do the 3rd gen. I just think for some period of time, some folks, because of financial constraints, or regulatory issues, or contract issues will not be able to shift once this comes out. You know, hopefully more people will move toward it, but I just mention that I think it is good to put some alternatives in here, but noting that people have to be aware of the limitations, and probably list that in their reporting.

Bernard Branson, CDC, Session Panelist: Thanks. I actually need to make a clarification, because we have a little bit of uncertainty around this, but I think what is really likely to happen with this algorithm is that it is going to probably be published someplace like the treatment recommendations are on aidsinfo.NIH.gov. so that it's not going to be 25 years before we revise it again. As things change, the idea would be to be able to update it as technology changes, and to point out where the changes are so that as opposed to being something that is as "set in stone" as an (*Morbidity and Mortality Weekly Report*) *MMWR* publication. So, I think to potentially partially address what you're saying, I think that, you know, we would be okay with saying "3rd gen is an alternative now." Once everybody has got a 4th gen, I think that similar to the problem with outdated tests being—you know, they stay on the market, but we don't necessarily want people to use them, and so I think that is something we hope to address in the updating process. Right?

Michele Owen, CDC, Session Panelist: Yeah, and I just want to add, I mean, you guys have seen—the document that was passed out is basically the outline and the actual recommendations, but I think everyone should know that when the full document comes out, there will be sections about limitations and data actually indicating why we are recommending or suggesting a certain algorithm.

Jenny McFarlane, Texas Department of State Health Services: This is a little bit off scope, but it is related to when it comes to implementation, but if there would be any way to link (Current Procedural Terminology) CPT® codes related to the testing, it would be very helpful for our providers when they begin to implement this in working with their labs and coding and billing staff.

Bernard Branson, CDC, Session Panelist: Do you know about LOINC codes (Logical Object Identifiers Names and Codes)? (Jenny replies "yes") The issue of coding, I think we can potentially talk about it, but I think it's unlikely that we would end up putting codes in, because I think that the 4th gen code was just approved as of January of last year, and they keep changing. So, I think we will end up coming up with some implementation guidance, which I think is what you're talking about, which is not going to be absolutely part of the recommendation, but will accompany it in order to facilitate people's using it. Do you think that would address what you're talking about?

Jenny McFarlane, Texas Department of State Health Services: Yes, and as you know, I mean, I just got off the phone with the Billing and Coding Work Group that Pascal is leading, and this is one thing that we hear from clinicians when it comes to entities, whether it's a hospital system or community health center, needing to know how they go about billing for this and what the appropriate codes are for billing. So, an outline, or even just working with Pascal—of course, I know you do already, but in assisting with building this guidance document. Thank you.

Bernard Branson, CDC, Session Panelist: In terms of what we're talking about, we still will welcome comments on any of this, but I do want to mention the next part of the recommendation is that basically specimens that are repeatedly reactive on initial immunoassays should then be subject to a test that differentiates HIV-1 from HIV-2 antibodies, and so we can sort of talk about both of those recommendations. I don't mean to do anything to people who are already in line by changing the subject, so go ahead.

Kama Brockmann, California Department of Public Health, Office of AIDS: My only conflict is I'm just trying to solve this for California. But, I think this might be more generalizable, and again, I'm a program person. The (Clinical and Laboratory Standards Institute) CLSI recommendations came out and there were 6 algorithms. I think what I hear you saying is that when the CDC comes out with their recommendation, it's just going to be this one, which was similar to the first CLSI algorithm, and so that's going to be the only one that the CDC recommends in this round. And so that's one question, and then the second question is: Is the APHL recommendation going to be concurrent? I'm trying to figure out how to write a regulation or law that doesn't depend solely on a CDC recommendation anymore, and so if I could say something like nationally—and if this is recorded—I wouldn't be—I can't be seen as like saying I'm going to do regulation or law, but if I was going to make a recommendation for the State of California—I always forget that these things are recorded.

Bernard Branson, CDC, Session Panelist: Does California still require 40 hours of training for finger sticks.

Kama Brockmann, California Department of Public Health, Office of AIDS: It does not. That was a law that we were able to change.

Bernard Branson, CDC, Session Panelist: I was thinking that's like 8 hours per finger.

Kama Brockmann, California Department of Public Health, Office of AIDS: No, it doesn't, and that's a law that it took us like 5 years to change, and so that's why I'm trying—

because we can't change law and regulation every time something different happens, and so we're trying to figure out how to get the broadest . . .

Bernard Branson, CDC, Session Panelist: What I can say is that our intention is to write this up as a preferred algorithm. Obviously, there are other tests that remain on the market that we cannot preclude them from being used, and similar to our limitations, obviously, some of these assays are not available for specimens other than serum or plasma. So, we are not going to say, "This is how it is. This is the only thing you can do." We are definitely going to make a strong statement saying, "This is what is preferred."

Kama Brockmann, California Department of Public Health, Office of AIDS: Along with the alternative?

Michele Owen, CDC, Session Panelist: I just wanted to say one thing about the CLSI document that I think sometimes gets lost in translation, and that is when the CLSI document was written—and I was actually one of the authors, so I think I can say this—we had to make it more global. It couldn't be just for the US, so the mandate when that document was written that it had to be not just for the US, but outside the US.

Kama Brockmann, California Department of Public Health, Office of AIDS: And I'm all for that. I mean, I'm trying to figure out if I can just say—you know, reference nationally recognized organizations, which hopefully can in include CLSI, CDC, and APHL.

Laura Wesolowski, CDC, Session Panelist: They won't be coming out with separate guidance. So, they're actually working with us.

Kama Brockmann, California Department of Public Health, Office of AIDS: So, they'll come out at the same time. That was my question actually—they'll be somewhat concurrent. Okay, great. Alright, thank you.

William Meyer, Quest Diagnostics: Thanks for judiciously working through all of these points. First disclaimer, I do have a salary from Quest Diagnostics, and the second disclaimer for my employers is my comments are my own and not Quest Diagnostics. As we go from when all of us who are old enough to remember just the rotary phones to probably 25 different cell phones, we're wrestling with all the different permutations and all the developments that have occurred in the last 30 years with diagnostics. And I know that you're going to have likely a preferred algorithm, and then maybe some alternative ones, and as Bob has pointed out, we need to have some flexibility just like in our cell phone selection. I have two suggestions: One, we in this room are more attuned to interpreting multi-test algorithms and the ultimate conclusions. But, the readers of the laboratory reports may not be in tune about how to conclude different conclusions from different combinations of multi-test algorithms. So, as we carefully design the multi-test algorithms, I think we need to carefully design and specify the content of the wording of the laboratory report, so that New York and Monica Parker doesn't wrestle with this for six months, and someone in Texas at Quest comes up with its own interpretation. So that as you release the algorithms, actually specify the language that should be reported along with different combinations of results, including potentially a conclusion line which puts together the individual components that went into that series of test results. The second thing is if we limit—excuse me, if we present alternative algorithms, which we know some of them at least may not be as sensitive at detecting early infection, then we should actually state that in the final report—not just in the limitations, like on the back of the package insert, or in the back of the CLSI document, but in the actual answer, so that the clinician that's reading it will know if the patient is more likely to be an early infection and might, therefore, need to go to some other assay to identify, for instance, early infection, which would not be as readily detected by a 3rd generation algorithm.

Bernard Branson, CDC, Session Panelist: So, in context of the second statement, I think what I'm hearing you say is if we talk about alternatives, such if a person uses as a second assay one that doesn't identify HIV-2, which is one of alternatives here, the report should say, "A limitation is that this did not test for HIV-2" or "A limitation is this may not detect acute HIV infection," and you are encouraging us to have that as part of the recommendation.

William Meyer, Quest Diagnostics: And including to the actual language for the results, because remember, the folks that are reading the report, and hopefully actioning on that report, may not be quite as sophisticated as many of the folks in this room, and they're the folks that have to translate that finally to action, or patient care, and / or information for the patient themselves. So, we're increasing the complexity of our multi-algorithm and increasing the complexity of how to interpret those results, and we need to not just say "Do this" or "We recommend this," but, this is the language that should show up on the laboratory report so we can have unified presentation and not have it interpreted differently from one group to another group. Thank you.

Evan Cadoff, UMDNJ - Robert W. Johnson Medical School, New Jersey: I still have a rotary phone for emergencies, because sometimes you have to go back to old technology, and we needed to use it last month. I guess I'm still a little confused, because on your earlier slide with the algorithm, you said "first screening" and just getting back to the question of screening for HIV versus diagnosis, and so I—and how you intend to use this, and whether this is supposed to replace the screening algorithms, because you do talk about this superseding the confirmation algorithm for positive screens from the 2004 recommendations when they're discordant, and you also then are talking about saying that we should start with the 4th generation, is that for confirming a rapid? But, you know, to say that we should do a 4th generation for everyone who is already 3rd generation positive, why can't we just do a 3rd generation confirmation rather than a 4th generation confirmation if they're already 3rd generation positive? And, so, right, I mean, you want us to just start with the 4th generation, but they already have a 3rd generation positive, why should you insist that we start with the 4th gen and have that extra expense depending on the predictive value of our first results? You know, we have about 90% plus confirmation on our first positives, so if this is going to be a more expensive algorithm for us to do extra 4th generation testing on all these people who are already 3rd generation positive, we're not going to be picking up 4th gen—we're not going to be picking up extra acutes if the people are already antibody positive to being with, so why do we have to go through this rather than just saying, "Well, maybe we'll have to do some extra NAT on those false positives?" That might be cheaper for us. So, that's a way, too.

Bernard Branson, CDC, Session Panelist: This is something actually we're very interested in feedback on. Michele and I probably have received more comments about this particular aspect of the recommendation, so just to contextualize it, we are making recommendations for laboratories in this guideline. And what we are making in this recommendation is saying that if a specimen has not been previously tested, or if a specimen has been previously tested and is submitted to a laboratory, the laboratory should follow this algorithm. Now, the difficulty is with what else we should tell the laboratory. We can't say "Don't start with a 4th generation," because if you did a 3rd generation and they do what we're recommending as a second test, which is a 2nd generation antibody test, that may be negative in the person; whereas, the 4th gen would be positive, then they could end up stopping there. And, as I think you've mentioned, one of the concerns that we had was that we don't want people to basically have to do a NAT on every false positive rapid test by not going through the algorithm. And so, any other input on that would be very helpful.

Evan Cadoff, UMDNJ - Robert W. Johnson Medical School, New Jersey: Yeah, that should be up to the laboratory to figure out the cost. So, you're not going to then also withdraw the point-of-care starting algorithms that have been out there? Because this sort of sounds like you are.

Bernard Branson, CDC, Session Panelist: The recommendation that we're talking about, the 2004 recommendation, was one to laboratories that said if a person had a reactive rapid test, they should not stop with a non-reactive, and that was during an era and there is a table in there when the Vironostika® was the prevailing EIA and many of the rapid tests were more sensitive than the EIA. We are now in a situation where the screening 4th generation immunoassay is more sensitive than any of the other point-of-care tests we are aware of, and so that is the reason we were planning to withdraw that recommendation.

Evan Cadoff, UMDNJ - Robert W. Johnson Medical School, New Jersey: As long as the test that you are starting with the laboratory is at least as sensitive as what was used in point-of-care, that should be okay?

Bernard Branson, CDC, Session Panelist: Well, more sensitive is what we prefer.

Lucia Torian, New York City Department of Health: I'd like to follow up on Bill's comment about giving the clinician guidance. It's absolutely critical that both the laboratories, and even in some cases with input from the public health department, talk to the clinicians, inform them, give them information about what the meaning of the test is, and what their ultimate interpretation is. We have a great illustration of a failure to follow-up in a laboratory in New York City, which deployed 4th gen and did not apply the same principles that we apply for 3rd gen testing where we have a discrepant Western Blot, and that is either go on to a nucleic acid test for confirmation or for sorting out the discrepancy, or call the patient back and get another specimen. A week later, the specimen is going to have seroconverted. You're in much better shape than you are sometimes then when you've tried to use the original specimen. We had a couple of acute HIVs that were not picked up because the 4th generation positive was followed by a negative Western Blot. There was no notation to the doctor that the patient should be called back and another specimen was needed, that a nucleic acid test was required. The laboratory had apparently never even done this with 3rd generation testing, which we all thought was just a basic principle of life, that whenever you have a discrepant test, that you'd follow it up with another—with a test of time or with a nucleic acid test. So, it's really critical that we give good interpretive guidance to clinicians who people have said over and over again don't necessarily know all of the receiver operating characteristics (ROCs) of the tests that we're deploying, and there's a constant influx of new technology that may be very confusing to them, and basically call the patient back, get another test, follow-up with something that's going to be a tie breaker. And if there's any information that we can provide in the interpretive report or any follow-up that the public health department can do on these discrepant tests, negatives, or indeterminates, we should "step up to the plate" and do it.

Bernard Branson, CDC, Session Panelist: Lucia you should have probably confessed your conflict when you got up. Lucia was responsible in New York City for issuing the Health Advisory to all clinicians about, what, 6 weeks ago, saying that if you do a 4th gen and you have a negative follow-up test, don't stop there, right? What we will probably do is number one . . .

Lucia Torian, New York City Department of Health: I wasn't thinking of that exactly as a conflict.

Bernard Branson, CDC, Session Panelist: I wanted to give you credit for that. But, I think what I'm hearing you say, and what I'm hearing Bill Meyer say, is that when we list the alternatives, we should clarify the limitations that are associated with them, and that we should include something that basically says the lab can't do it all on just one specimen, and so follow-up may be an appropriate step to take in the case of discrepant results.

Laura Wesolowski, CDC, Session Panelist: But, I think Bill was also saying that in the laboratory reporting, we put the limitations associated with the tests that were done.

Bridget Anderson, New York State Department of Health: More of a— it's not really a disclosure, but a disclaimer, I'm not from the laboratory, I'm from epi, and that will help in understanding my comment, which is really picking up on what both Bill and Lucia have commented on. There is the issue of clarification in the report that goes to the clinician. There is also the reporting stream that laboratories are obligated to give to public health surveillance programs, and it's important to remember that unlike the previous algorithm in which a single test, the Western blot, confirmed someone for CDC surveillance purposes, it's now combinations. And, at least in New York State where we do have reporting of all viral loads, we—it's more than just the conclusion of the algorithm. There are times where pieces of it must be reported, so not just the final conclusion, and so I think it's important to keep that on the table that there really are two reporting streams that are at times different.

Bernard Branson, CDC, Session Panelist: And if I can comment on that, we did not give you all of the draft, just the recommendations. There is going to be the section in this document that talks about reporting, both reporting to clinicians, which is to address Lucia's and Bill's point, and laboratory reporting to surveillance systems, which is to address your point.

Bridget Anderson, New York State Department of Health: Great, and the presentation that Monica gave yesterday about, you know, what New York State has been doing,

we are very clearly laying out the differences and, you know, trying to ensure that there's clarity in what the expectations are.

Bernard Branson, CDC, Session Panelist: Thank you.

Michael Busch, Blood Systems Research Institute: My question, and I think I already provided my disclosures, yeah a couple of points, first just what an incredible meeting and how much progress, and I want to congratulate you guys, Berry, Steve. And you know, from our discussion in the beginning that this meeting might not have happened, that's just criminal. This is one of the most important—I go to lots of meetings—this is one of the most important, informative meetings that we have, and if there's a mechanism that you can share with us the names of the people at CDC who we should be writing to, because I'm ready to do that.

Bernard Branson, CDC, Session Panelist: jmermin@CDC.gov

Michael Busch, Blood Systems Research Institute: Can that be sent in an email to the attendees? I'm serious, because I think a quick response would have a huge impact, hopefully, in continuing this meeting. And also, I really liked Mark Pandori's tribute to Brian, and I think this should be part of this meeting going forward. There should be a recognition, because we really are hitting the point where a lot of people are retiring and should be recognized. To the algorithm, one point, generation, I don't think FDA actually talks about generations of assays, so you obviously need to specify that.

Bernard Branson, CDC, Session Panelist: There is a definition statement actually in there that will define generations, and the definition of "acute infection" as is used in the document.

Michael Busch, Blood Systems Research Institute: In the concept of going to a 2nd generation after a 4th, and sort of explaining it, you're trying to purposely capture recent seroconverters in a sense, and you know, that's not the way—if we, CDC, or for broader reasons as Chris discussed, you know, if we want to identify people who are infected within the prior,

you know, two to three months, we should be doing reflex testing that can do that. And I think your application and specification of the 2nd gen test actually is very restrictive if we—a second, you know, equally sensitive, or, you know, if you want to do a less sensitive test to discriminate recency, a simple designation of a Multispot or something, isn't the way to do it. And it also locks us in from things like Geenius™, you know, is that a 2nd or 3rd generation? You know, that terminology I think is—and the general principle of trying to incorporate this diagnostic algorithm a less sensitive antibody test in order to identify recent seroconverters, I think—I support identifying them, but I think that's not the way to do it.

Michele Owen, CDC, Session Panelist: Okay, so I'll make a couple of comments. I think it is helpful based on the surveillance definition that we're trying to support, but I also think it's not that we're just necessarily—once again, we're not specifying one test. It's supposed to do two things. It's supposed to differentiate one from two, and my certain understanding is that tests coming will likely do that, so we're not just doing, you know, Multispot. And as far as identifying acutes, I think if we really knew that we had a test that we could easily reflex to an individual person, it might be a lot easier to do that. And while I certainly agree that Chris's data is, you know, encouraging, I think we actually have some encouraging data at CDC as well. But, we're not there yet, so we're trying to do the best we can with the technology that's actually out there at the moment. And, like Bernie said, the reason for trying to publish them in the place that we're going to publish them is that we can be proactive in the future, and revise much sooner than 20 years.

Bernard Branson, CDC, Session Panelist: And actually, Mike, you're probably smarter than I am in this whole area, but the whole issue of differentiation assays, I'm not familiar with whether we can differentiate in immunoglobulin M (IgM)—whether they're type-specific assays. So, that was part of the intention here, was that based on our current knowledge and the currently available tests, we wanted to do two things . . .

Michael Busch, Blood Systems Research Institute: Now when you define it, is 3rd gen—is that the antigen sandwich?

Bernard Branson, CDC, Session Panelist: Our definition is going to be IgG sensitive versus IgM and immunoglobulin G (IgG) sensitive, so as opposed to the technology, it's got to do with—as we tried, as I tried, at least, to write this recommendation, as I went through saying IgG sensitive versus IgM and IgG and antigen sensitive, it just got longer and longer.

Michael Busch, Blood Systems Research Institute: That IgM discrimination, if you go back to the original Gallardo paper, the first so-called 3rd gen, I mean, that's a real—that's not really documented. If you look at any of the FDA trial data, the fact that these tests can pick up IgG—very little isotype specific work has been done. And with the chemiluminescence, I mean, the sensitivity of these tests of these tests isn't attributable exclusively to IgM detection. I think that it's overall great stuff. I do think—the other thing, the specificity of the final algorithm, I mean, some of the data looks great, but then that other table you showed had like 85%, and I guess I don't understand why those numbers were so low.

Bernard Branson, CDC, Session Panelist: Well, those were just—those were all only Western blot indeterminate and negative after repeatedly reactive assays, so that 85% has a denominator that is very skewed.

Monica Parker, Wadsworth Center, New York State Department of Health: No conflicts. First I want to thank Bill for his comment, and I agree that all of this sort of "reinventing the wheel" seems a bit inefficient, and if we could somehow figure out a way to facilitate consensus language for these interpretations, I support that idea. So, that's one thing. And then regarding the rapid test then feeding into the laboratory and beginning with the 4th generation IA or the, you know, a test that is more sensitive than the rapid test, I agree that that's probably a good practice. But, we also need to recognize the very stringent specimen requirements for these 4th generation tests. For the Bio-Rad one at 48 hours, actually in our case where a lot of samples come through the mail, that is very problematic. And so rather than UNSAT (unsatisfactory for review) a sample that's coming in for a rapid test and being able to do the 3rd generation on those, and continue with the Multispot, and if necessary the NAT, and we know that works really well, and we've been doing that for a long time, so that would be something just to consider. And just one last quick comment just sort of to defend ourselves so

you don't think we're all crazy about this Multispot scoring, I just do want to mention, part of where that comes from is that one of our lab services is doing the diagnostic testing on all of the HIV-exposed babies born in the state, and we run a Multispot on all of those and we get multiple samples over time, and that gradation has actually been really helpful to watch antibodies, and is also an important quality control result from time-to-time it has really played. So that's part of why our lab has sort of starting doing that.

Bernard Branson, CDC, Session Panelist: Before you step away, to try to paraphrase your first comment, I think that what you're suggesting, or what I'm hearing, is that we potentially put a limitation statement in terms of the algorithm about the specimen handling or requirements such that if it—if you receive a specimen that is not suitable for 4th gen, but might be suitable for 3rd gen, you don't do nothing. Is that correct?

Monica Parker, Wadsworth Center, New York State Department of Health: I think that's part of it. Or, if all you're doing is rapid test referrals, and you're using a 3rd gen that's going to be—while we—until maybe we have a 4th generation rapid test, that that would be acceptable to use a 3rd gen.

Bernard Branson, CDC, Session Panelist: The reason I sort of mentioned that when I presented Silvina's slide with respect to the Determine Ag/Ab combo tests that is before the FDA. We anticipate it relatively soon, and so we are uneasy—I am uneasy about essentially basically saying, you know, "Oh, it's okay. After rapid tests you can use this less sensitive tests," because it's going to change so quickly that the algorithm will be outdated before that. And I want to say that I admire all the work that Wadsworth does, and I did not mean to say anything about your spot intensity study.

Monica Parker, Wadsworth Center, New York State Department of Health: It was funny.

Michele Owen, CDC, Session Panelist: That's okay, Monica. We've actually done it at CDC, too. I'll make the disclaimer.

Monica Parker, Wadsworth Center, New York State Department of Health: There's more than one crazy here.

Kevin Delaney, CDC: I don't think I have any conflicts, but I'm not sure. The second main recommendation and also the second alternative, we talk about differentiation assays, and I think even Lucia might agree that there are certain places where looking for HIV-2 may not be cost-effective. My bigger concern, though, is with the wording of the second alternative and the word "supplemental," and I know there are package inserts in screening tests that say that we need to use a supplemental assay, but I don't think there's any data actually other than for blood screening that's in the regulations. I think that word is there for no other reason than it needs to be there with the donor screens. And so I think as the second test, if we can't differentiate, would we consider using any other test that is not IgM sensitive?

Bernard Branson, CDC, Session Panelist: I would appreciate hearing other people's comments on that. The issue of saying "supplemental" as an alternative actually was carefully chosen, because for example, if you use a Western blot as an initial test on people not after an EIA, I think you get considerably different specificity from it. And so the idea of the sequence of tests in the order selected has to do with the evidence that we have with respect to the combination of tests in that order, so if there are other comments on that. I don't think we are yet comfortable saying "You can use anything as the second test," and if people have evidence or comments otherwise, we'd very much appreciate hearing them.

Michele Owen, CDC, Session Panelist: Yeah, and I would just say, I mean, there probably are tests out there that could be—that were listed as supplemental—that could be the first test. But, if there's not data available to support that, like Bernie said, I don't think we're comfortable saying it.

Kevin Delaney, CDC: I wasn't saying to use the supplemental test as the first test, but that tests that aren't indicated as supplemental tests, that are indicated as other screening assays, or as rapid tests, that those could be the second test in the algorithm is what I was suggesting.

Kathleen Krchnavek, Wisconsin Division of Public Health: I have no conflicts. As someone who works primarily with testing sites, my hope is that the recommendations will help with messaging to clients around repeat risk—recent risk and repeat testing for negatives. And also, if this algorithm is now focusing more on sensitivity, if the first two steps result in a positive result, but we're concerned that there might be some possibility that someone may come up really false positive, whether the provider should be stating that or should be simply stating that, "You're HIV positive," because there could be concern that that holds out more hope for the client that this is a very rare false positive that—so, I guess the direction as to whether a 4th gen and differentiation assay, both positive, you're positive, or whether we need to share that message that in our clinical workup it's possible that we may find that you're not infected, although this would be considered a rare instance, so helping with the messaging of giving that test result and repeat testing.

Bernard Branson, CDC, Session Panelist: So, this is right now the way the recommendation is stated, that people should be considered positive for antibodies and should initiate care. This is part of the—actually, the second part of the statement is from the *Department of Health and Human Services (DHHS) Antiretroviral Treatment Guidelines* that say that's what should happen when a person goes into care. I'm not—the one question I guess is whether we should make a further recommendation about what to do in the event the viral load is negative. Is that perhaps what you're suggesting?

Kathleen Krchnavek, Wisconsin Division of Public Health: Yes, you know, although I would say that, you know, I guess from my perspective, for testing sites that's probably not—I mean, that would be something that hopefully clinicians would—specialists would know what to do. It seems here that it's clear enough that we should really not provide any nuance at the level of giving a test result at a test site, "You're considered positive. We need to get you into care."

Laura Wesolowski, CDC, Session Panelist: You have a concern that they wouldn't seek care.

Kathleen Krchnavek, Wisconsin Division of Public Health: Exactly.

Bernard Branson, CDC, Session Panelist: This is one we heard it from Barbara, we heard it from Lucia, and now, Kathleen, we heard if from you, that we should include some statement in there about basically what to do if it is not entirely conclusive that—is that correct from other folks?

Niel Constantine, University of Maryland School of Medicine: I've no conflicts in life; however, I'm very surprised that we have to state whether we have conflicts to ask a question or make a comment. I'm surprised at that. Regulations are getting tough. I have two comments. Both relate to the side of the algorithm where the ARCHITECT® is positive and the Multispot is positive. The conclusion written underneath here is HIV-1 or 2 antibodies present, and I'm wondering how physicians will interpret that. When we do classical EIA Western Blots and we report those results, we say, "This is consistent with HIV infection," and that's pretty definitive. In fact, even on the RNA testing in your algorithm at the bottom, you have "HIV Infection" rather than "RNA Present." So, I'm just wondering how they're going to interpret that. We're going to call them and they're going to say, "Is this is a confirmed result?" and I want to know what kind of answer we're to give them on that. That question relates to the second part of my second comment on the same issue, and that is: How often do we see false positives when we have a positive ARCHITECT® and positive Multispot? There've been several presentations, including one you're on, Bernie, that show that when you have double positives like this, sometimes, the RNA tests are negative for a variety of reasons. Most of the presentations were, "We don't know why. We couldn't follow up. Maybe he's on treatment." But, do we really know collectively what the false positive rates of those two tests are together? I would imagine it would be pretty low, but do we know? And if we do know, perhaps we ought to state that also in the conclusion as to whether this is 98% specific when you use this together, meaning 1 out of 50 people are going to be false positives. Because it's not the classical Western Blot type result where people have a lot of confidence in physicians, for example, I'm wondering what HIV positive antibodies as a result is really going to mean to them.

Bernard Branson, CDC, Session Panelist: What I can say is that your comment causes me to lean in the direction of changing the one place that says "infection" and say "consistent

with acute infection," because I think that this is a real dilemma for the laboratory, which is I think you can say that antibodies are present. I don't think you can absolutely tell given the exact circumstances you point out, which is that antibody positive, RNA negative people—I don't think a laboratory can conclude a diagnosis for them.

Michele Owen, CDC, Session Panelist: Right, but, I think it kind of goes back to Bill, and Lucia, and other people's comments about the messaging on the report and what we think it means. I think—do you agree, Niel, that if we have some sort of interpretive statement of what we think that being positive for antibody means?

Niel Constantine, University of Maryland School of Medicine: Sure, absolutely, but the problem is when you get these two positives, you don't do RNA testing. So, you can't really say, you know, definitively . . .

Michele Owen, CDC, Session Panelist: Well, right, but even RNA doesn't tell you definitively.

Bernard Branson, CDC, Session Panelist: Well, but, we are recommending—and this is the statement that says if you have those two positives, that you do initiate care and laboratory testing. I mean, that is part of the recommendation. It's recommendation 3.

Niel Constantine, University of Maryland School of Medicine: Is that going to be with the algorithm? Okay, so you're just saying with two positive results, they should continue testing after care.

Michele Owen, CDC, Session Panelist: Clinical follow-up.

Bernard Branson, CDC, Session Panelist: Yes, we think that with two positive results, you should initiate care, which includes—and this is again a statement from the *Antiretroviral Therapy Guidelines*, which says this is part of the initial evaluation of a person with a positive result.

Niel Constantine, University of Maryland School of Medicine: Okay, so the question is: Are we as confident with giving that initial result, antibody positive / two tests, as being enough to label that subject as positive for antibodies? Again, them thinking "confirmed" probably. Even though you're going to get them into care later, are we as confident with that as we are with an EIA Western Blot positive?

Bernard Branson, CDC, Session Panelist: I think you notice we were very careful to not use the term "confirmed" anyplace. As a Catholic kid, you know, you got confirmed when you were 14, and the Bishop slapped you on the cheek. That's sort of the second part of things that happen. I think that in this, I am willing to have comments from other folks that basically what we're talking about is what laboratories can do, and as the package inserts say, "These are aids to diagnosis." I think we would like to avoid the prescriptive language in 1989 that said, "It has to be repeatedly reactive, and nobody can get a result that's positive until you can go through this sequence," recognizing that we now have a variety of tests with different levels of sensitivity, and we have molecular tests, all of which need to be brought to bear in order to come to the decision of a diagnosis, which is way different than just the conclusion on the basis of antibody tests.

Niel Constantine, University of Maryland School of Medicine: Might I suggest you consider as a result—we don't want to say, "Presumptively consistent with HIV infection," but you could certainly say, "Preliminarily consistent with HIV infection. Follow-up testing required." Something to that effect, until we know the false positive rate of those two tests together. I mean if it's 100% specific, then you don't need to say that.

Bernard Branson, CDC, Session Panelist: I think the real difficulty is that we are never going to know, because it depends on whether you use the Abbott test, Bio-Rad test, or the Ortho test, or the Siemens test and what you use as your differentiation assay kind of thing. I mean, I think we will continue to generate that stuff, the data on the combinations of those things, but I don't think it can actually be part of the recommendation.

Lixia Liu, Indiana State Department of Health Laboratories: I don't have any conflicts, but a current conflict is inability to comprehend the algorithm. I have two questions to ask. The first one is actually, Dr. Werner, I agree there are many labs still doing a 3rd generation, so for the NAT test for a pooling test has been discussed during the meeting, so what is the role for a pooling NAT test for the alternative algorithm?

Michele Owen, CDC, Session Panelist: So basically, it's really the same as if you started with a 4th gen. So, you know, if it doesn't confirm with—or if the supplemental test isn't positive after you do the 3rd gen, you should still go to NAT. Is that the question you were asking? Oh, pooled NAT. I guess that is somewhat independent of what you guys decide to do. To me, I think it—the number that you would be actually doing at that point might not be that huge, so I think doing individual would probably be the best choice, but if you can truly pool, and deconstruct, and get the results back—because I think that part of the issue with pooling is giving the results back as quick as possible. If the lab wants to go through the process of validating a pooled, you know, approach that's been validated and they're okay with, it's fine. It just seems to me that it adds another step.

Bernard Branson, CDC, Session Panelist: Well, I mean, I think if I can respond, what again we're trying to do here is issue a recommendation for a laboratory diagnostic testing algorithm in terms of the currently available tests. We have certain restrictions in terms of making recommendations for off-label use. Pooled screening, I think, is only approved for blood centers at the current time, which is why the PROCLEIX® has a different name than the APTIMA®, because of the validation that has been done there, and so we are trying to cover the main circumstances that people encounter. I don't think we can do every permutation that people might choose to do. The pooled screening that you're talking about is really I think something that, you know, we would not want to encumber Quest, for example, with saying, "You have to take all of your antibody negative specimens and pool them every three days."

Lixia Liu, Indiana State Department of Health Laboratories: My second question is about the Multispot testing algorithm used as a supplement test, and also you do not specifically say what specific—but as I remember Multispot, the challenge was because the intended use

wasn't for confirmatory. So, my question is since so many new tests are on the horizon, so what if we got a new one that is as good or better as Multispot? So, do you keep that in mind when doing a validation of an FDA approval—that confirmation part is already included?

Bernard Branson, CDC, Session Panelist: We have been actually having discussions with both the manufacturers and the FDA to make sure that the language in package inserts doesn't end up being restrictive in terms of what can be used. We do anticipate things will continue to come out. It's one of the reasons why we also, I think, anticipate doing this recommendation in a place where it can be updated more frequently, but we would not obviously be making any brand-specific recommendations.

Joanne Stekler, University of Washington, Public Health Seattle-King County: I don't think I have conflicts to disclose, and I remember rotary phones, too. So, I have two areas that I want to comment on. The first is related to the language issue that you have been—Bill brought up, and people have been discussing just how complicated that really is, and sort of—I've been working with Bob and Joan in trying to get appropriate language, and every time you make a change, people do something wrong. We've certainly had examples of people who got initial screening tests, and a negative Western Blot, and said, "You're not HIV infection," when it was really acute infection. We have a recent example of someone who had a positive Determine Ag/Ab Combo and a negative Multispot that got reported as "presumptive antigen," and the clinicians told that 80 year old person with no risk that they probably had acute HIV infection. And so, it's complicated is really what my caution is as you think about doing that language. A comment for—now I can't remember who just—it was Niel, about positive versus infected, and when you're doing diagnosis in a lab, you have a single blood specimen that's there. There have been mix-ups that have occurred. You want to—you don't want to tell someone, "Absolutely, positively you're HIV-infected." These follow-up tests need to happen. We sort of wonder whether or not, you know, the primary infection clinic at my research clinic serves as a reference for people to try and help solve some of these complicated testing situations, so for most people who are testing positive through the algorithm, it's not going to be complicated. You're going to be able to generate language. But, there are going to be some people who are 4th generation positive, supplemental test positive, who end up having

undetectable RNA, and is that person a false positive? Is that person just a primer mismatch? And I think it's really helpful to have resources available, and I don't know if you would be willing as CDC to have a single resource for these labs to say, "If you have questions and you can't resolve them," you know, because there's this and there are other things, and I'm actually going to give you even more work—because I think a lot of this is Seattle-King County is really different, Seattle is really different than New Jersey. Sort of how you interpret your test is going to depend on your pre-test probability, and it's often very population-dependent, and I think how we interpret this is really going to depend on what your population is. I think those are my only comments related to that topic, and then while I'm just standing, I'm going to put a plug in for screening for acute infection. And I think it's really nice that the algorithm is moving in that way, and that we're starting to get people more on board. But, just sort of to put this into a little bit of context that screening for acute infection is only going to become more and more important, particularly as we get more and more people tested in this country, and testing more frequently, that just by chance we're going to have people who are testing in that window period. And as we're treating more people with established infection, the proportion of all new infections that are coming from people who are recently infected is going to go up. Even if we can get those sort of total number of new cases down, the relative importance of acute infection is going to go up, so I think we're just "shooting ourselves in the foot" if we're implementing all of this testing, and linkage to care, and getting people on treatment if we are not simultaneously really focusing on getting the best test, which is what we've been doing here, and it's really nice. I think those are all of my comments.

Bernard Branson, CDC, Session Panelist: Joanne, I guess something I'm hearing from you is that perhaps we should do is indicate the limitation that, in fact, RNA is more sensitive than the 4th generation, and if we were to be screening for acute infection, we would obviously do both RNA and antibody as opposed to 4th gen, which is really the most cost-effective alternative, but not necessarily the most sensitive alternative.

Joanne Stekler, University of Washington, Public Health Seattle-King County: Right, and I even struggle with sort of if you're really—if you're trying—I mean, I agree with that absolutely. I would never propose that everybody in the country be doing pooled RNA

screening. I don't think that's a reasonable thing to do. But, I mean, even the question of if you come in and you're suspecting acute HIV, I would still recommend screening with a 4th gen, particularly if that person as symptomatic. They should be positive on their 4th gen. So, I don't—I mean, you could have a whole list of sort of papers of sort of what are the issues related to the algorithm.

Bernard Branson, CDC, Session Panelist: Well, the big thing that has come up a couple of times, and I know Bob Coombs quoted me on this, is the "test of time", which is that you can also just do a repeat specimen.

Joanne Stekler, University of Washington, Public Health Seattle-King County: Absolutely, but that's not the guidance you can give the lab. That lab has to give that guidance to the clinician, who may not necessarily be looking at the algorithm.

Catherine Humphries, Alaska Public Health Laboratory: My conflict is with really hot weather. Actually, I grew up in Atlanta, so I have the utmost respect for people that work at CDC and deal with this heat. Anyway, I like the algorithm. I guess my comment isn't really on that. But, I speak for low incidence labs that, you know, don't have genius scientists doing a lot of research. And I'm just curious, really it seems like what we need is the Multispot to have two more wells, one more control and a p24 well. And so I'm curious as to—well, I guess I'm just curious if that's been in development, or is there a reason why that can't be—why we can't have a 4th generation differentiation assay?

Bernard Branson, CDC, Session Panelist: What I can say is that they are under development, but we don't know whether or when it might be brought for FDA approval, obviously. I think Philip Cunningham from Australia talked about the fact that they do test for p24 antigen as opposed to testing for NAT in order to resolve it, and we're doing the best that we can with the tests that we have available to write recommendations that take that into account. Part of the CLSI algorithm was because Canada does antigen testing separately, and in the US, they don't. I'm sympathetic with your problem. I don't know how we're going to solve all of

the low prevalence kind of settings, so I think there's still going to be a need to resolve false positives.

Joan Dragavon, University of Washington: No conflicts, but I had a rotary phone and a party line.

Bernard Branson, CDC, Session Panelist: People do not need to acknowledge what type of phone they had. That's not part of the rules, okay?

Joan Dragavon, University of Washington: But it's brining up, you know, memories of my boyfriend calling and not only my family listening, but the neighbors also listening on the party line. So, it's therapeutic to say that. A couple of things, one in the algorithm, as you go down the right hand side, you specify RNA, and I'm wondering if what we could possibly do to have some sort of statement about the potential for off-label use of viral load tests in the context of this algorithm.

Bernard Branson, CDC, Session Panelist: Actually, that's probably bad shorthand. I think what we will say is "nucleic acid test," and I think that what the recommendation will say is, "FDA-approved nucleic acid test" in order to finesse the thing you're talking about. I don't think we're going to try to get into, in this recommendation, the issue of qualitative versus quantitative, because I think that a positive nucleic acid test is going to be sufficient. Is that what I hear you saying? Because there's also going to potentially be DNA. I don't know what's next, right?

Joan Dragavon, University of Washington: Yes, exactly, so to open that up, but also to give some support for being able to use the viral load assays, which I think is very important. And then also, on the next page on Number 4, for the HIV-2, that specifies DNA, and it would be really nice since there are two RNA assays available and there's no commercial DNA assay available as well, that could be opened up to be and HIV-2 NAT also.

Michele Owen, CDC, Session Panelist: Yeah, and we've had some discussion about that. I certainly have no problem, and I think it's certainly fine to say HIV-2 RNA, but with the caution that people know that oftentimes, like other people have said, that HIV-2 people do not have RNA. So, if the RNA is negative, that doesn't mean that they're not infected.

Joan Dragavon, University of Washington: I understand that, it's just the DNA is going to require another sample, so if we did the RNA test first on the original sample, we might be able to resolve that first sample.

Bernard Branson, CDC, Session Panelist: As one of two laboratories in the country doing HIV-2 RNA, we appreciate your comments.

Joan Dragavon, University of Washington: Thank you. I wasn't trying to drum up business. I was just really talking about the principle there. And then also I wanted to make sure that you are going to put some sort of caveat in there about participants in vaccine trials, and especially, you know, not just current vaccines trials but all of the vaccine trials that have gone on because a number of them have lasted for many years, and some of them are quite reactive in tests like the Multispot.

Bernard Branson, CDC, Session Panelist: And that statement is in there, and it's going to be "vaccine recipients" not "trial participants."

Elliott Cowen, FDA: I don't have any conflicts, at least financial. This is a very picky comment, and it's something I could have mentioned the other night when I talked about package inserts. In crafting the language, if you can go to the slide that was up before this that said Number 3, when we put together package inserts, we make a point of saying that results of tests are reactive or non-reactive, but the interpretation is positive or negative. So, that's something you should work in. The only reason I bring that up is if you leave the wording like this, "Persons whose specimens are positive on the initial IA" instead of "reactive," that might be confusing for people who are reading it very carefully. So, it's something that we made a point

of doing, so I just thought I could bring that up. "Reactive" is a result, non-reactive is a result, and "positive" and "negative" are both interpretations of the test.

Levinia Crooks, Australasian Society for HIV Medicine: I just really encourage you to do what you can to get some information on the results that are going out. We've done this for a number of years now with HIV results, and putting information out also to connect patients through to services for patients, and seeing that there's a main point of contact. Most recently, and I'm talking about the last 8 years, we've been running a project where positive results are followed up so that Philip in the lab or someone else is getting a positive antibody and confirming, they'll ring through to the doctors concerned, but also through to my agency, and we can offer the people who are not doctors who are giving those results back, because it's a different set-up, who aren't familiar with that support at the time. And we're finding really huge pick-up. We've only had about three people say they didn't want to do that, and they've found it useful.

Chris Pilcher, University of California, San Francisco: No conflicts. I wanted to raise something that you raised, Bernie, at your talk at the Conference on Retroviruses and Opportunistic Infections (CROI) last year, which we addressed in a poster, but that a lot of people are thinking about, which is the use of sort of rapid results reporting, which is feasible now using automated analyzers, particularly in medical settings. A lot of hospital labs are now installing the ARCHITECT®, for instance, and other analyzers are available, obviously. You can potentially return those results to somebody whose sort of stat tested on the ward in the emergency department (ED) or in a drop-in clinic setting for acute HIV infection, and you can potentially complete the first couple of steps—maybe the first step, maybe the first two steps, but definitely not the whole algorithm during the course of a patient visit, during an hour or a two-hour time window. And that's a real—this is sort of a testing space that has not ever been exploited and is really potentially a big opportunity for prevention. So, my question is just if you guys could tell us in the algorithms whether you're including any recommendations or any discussion of sort of at what point along the cascade of communication results to a provider, you know, potentially to hold patients or, you know, or if it is permissible. Because that's one of the

questions when you're talking about this sort of testing that I get, which is, "Well, I'm not sure I can report a single 4th gen result if it's not confirmed." So, if you could just address that.

Bernard Branson, CDC, Session Panelist: What I can say, and Michele can correct me if I get it wrong, but our intention is to basically recommend that people report out all results of the tests that are performed, and report out each result as it becomes available.

Chris Pilcher, University of California, San Francisco: Will that be clear in the recommendations? Because it would be fabulous if that could be clarified.

Richard Hodinka, Children's Hospital of Philadelphia: Just to make a comment on that, we do exactly what was just said. So, from the initial 4th generation on through, as the test results come out, they get reported, immediately available to the physician, next test is done, immediately available. We're doing it random access, essentially stat, while people are waiting in the ED or in the clinic. Because they are a 28 minute test now, you can just do them very quickly, followed by a quick Multispot or a differentiation assay, whatever it may be. And then I'll call and say, you know, "If necessary, the RNA test will be run at this time, and you'll have to wait this period of time to get that back."

Bernard Branson, CDC, Session Panelist: Thanks. Let me say that we also obviously have to accommodate public health laboratories, who I don't think we want them to be constrained to report out their EIA in the morning, and then report their next result in the afternoon, and the next result the next day. So, this would be permissive and not prescriptive.

Joanne Stekler, University of Washington: There also may be laws that prevent doing that.

Michele Owen, CDC, Session Panelist: And I also know some of the older package inserts actually, you know, that's something else we have to be mindful of, but we don't want to prevent it from happening when it is possible.

Susan Fiscus, University of North Carolina—Chapel Hill: Like Joan, I remember party lines. My question is—my assumption is, especially with this rapid turnaround time, that this—all of this is being done on a single specimen, and so does anyone worry about misidentification, and mislabeled tubes, and stuff like that? And I think it should be made clear on this, because if people are accustomed to getting a sample, and getting a result, and then drawing another sample to get a confirmatory thing, I think it should be made clear that you're doing all of this on one specimen.

Bernard Branson, CDC, Session Panelist: We're not sure that people will be. I know that certain laboratories, for example, will prefer not to do nucleic acid testing on a specimen that has been opened and has been tested for an antibody, and so I think we'll probably have to clarify that. But, what I also hear you saying is to put in a caution with respect to possible sources of error, and that it would be preferable to repeat a test. Again, our recommendations are intended for the laboratory, and the couple of comments that I think we have heard now have to do with how we need to communicate these to clinicians about what steps they need to take in that regard. Does that cover it, Susan? Not quite? You're not happy?

Susan Fiscus, University of North Carolina—Chapel Hill: No, I'm always happy. I'm just—there are rare cases of tubes getting mislabeled, and it's one thing if you're doing rapid testing, and the person is right in front of you, and you've got a result. And it may be less common in a hospital where—but, I'm thinking of the public health labs that are getting stuff sent in, and they have no control or little control over what's going on where ever the samples are being collected.

Michele Owen, CDC, Session Panelist: I think that some of that comes back to the thing that we're saying, that they appear to be antibody positive or whatever, and that they do need to actually go to their clinician to actually get the follow-up to do the actual diagnosis.

Jie Fu, New York Public Health Lab: No conflicts of interest. I have a comment on pooled NAT tests. Bernie just mentioned it's not suggested to do pooled NAT testing, and Michele mentioned as long as you do validation, you report, that's the key. So, I would like to

share our experience with you. We started pooled NAT testing in 2009, and since we switched to a MSM risk group, we can identify up to 0.7% positive rates. So, I don't have the calculation, detailed calculation; however, I think it's cost-effective if you just do pooled NAT and NAT deconstruction, and you still have a pretty good turnaround time. So, that's what I want to point out. I think it depends on which area you are in, and your rates, and high positivity rate, so it is still pretty meaningful to do pooled NAT testing. Thank you.

Bernard Branson, CDC, Session Panelist: We really want to appreciate everyone's patience here. I think that we'll take the last three comments, so nobody else can get in line except these guys, so we can move on to our very final session.

Thomas Knoble, San Francisco Department of Public Health: I have no conflicts of interest. I want to just thank the scholarship process. This is always such a great way for me learn information, and then take that information back to the communities that I work with and disseminate that information. That being said, with what's going on with point-of-care testing and the changes that are happening, I want to be part of the solution on how to disseminate that information with regard to a rapid testing. And I'm not sure if there is a mechanism at the moment, or if there is an idea of a mechanism or anything along those lines, and if there's not, how do we make that happen related to rapid testing and programs? And also, just with regard to these changes that you guys are discussing, how do we package that information for people who aren't laboratorians, not only clinicians, but people who are working in more lay settings.

Bernard Branson, CDC, Session Panelist: First of all, with respect to rapid testing, there is, I am promised, a separate process with respect to program guidance that will address certain things about rapid testing and the options in terms of rapid test algorithms that are linked to care and what people ought to do, depending on what their circumstance is, recognizing that, you know, we anticipate really within the next six months there may be several other rapid tests that will be approved, and so it's hard to keep up with that. And then, I think we very much hear your message: we have to make sure, as I think other people have said, to communicate not only with clinicians, but to other people what the interpretation is of these recommendations as they differ from what we've been doing in the past.

Jenny McFarlane, Texas Department of State Health Services: I didn't mention before, but I will now, I have no conflicts. But, one thing that through this discussion is making me a little bit anxious is the language on Number 3 is I think we underestimate the familiarity and roteness that clinicians got into with the Western Blot and "Yeah, I have confidence that you are HIV positive." And thinking through this and hearing the comments of, "Yeah, considered positive for HIV-1 or HIV-2 antibodies," gosh, most of our diagnosis is going on in clinical settings and medical settings. It's strong next in sexually transmitted diseases (STD) clinics and then our counseling and testing sites. So, really, I think the education portion is so important, and I will really plug to the medical schools who are here who are teaching students and residents, add this to your curriculum, please. Add the curriculum of routine testing, period, and then interpretation of test results or being able to give results effectively. And I want to make a plug, or encourage this discussion to occur with our friends at University of California, San Francisco (UCSF) who run the Warmline and making sure that they're available for clinicians when it comes to interpretation of results. And I'm glad that Cindy Getty has been here for training and the importance of this, and for our dear friend Jewel at the CDC and the training that you all do, but also down the road of our other partners that support routine HIV testing, such as Substance Abuse and Mental Health Services Administration (SAMHSA), Ryan White, et cetera. And lastly, what does this mean when it comes to the issue around the high risk populations, our greatest risk populations, who are savvy to post-exposure prophylaxis (PEP), and what will this mean? Do we know what the influence of PEP on this will be for our men who have sex with men (MSM) who are getting their hands on TRUVADA® (emtricitabine/ tenofovir disoproxil fumarate) and testing regularly and they think, "Oh great, you know, I can get this 4th gen test and I'll know sooner if I'm acutely infected. Then I'm going to go party." So, for our friends in research, and the manufacturers, and whomever, the influence of PEP in these tests, and please put that in your thought when it comes to research and design, and whatever your language is. Again, thank you very much. Thank you to the Scholarship Committee, because we couldn't be here without it, and this has been fantastic.

Kimberly Hibbs, The Division of Consolidated Laboratory Services in Virginia: I have a question related to public health laboratory testing. It's great that it has on here the

alternative for sticking with 3rd generation for those of us that may or may not be able to get funding to go to 4th generation at this point, but my question is, it doesn't really clearly tell me what, if any, changes there are to the actual treatment of negative samples when they're run on a 3rd generation EIA and they're negative. Apart from saying that it may miss acute infections, it doesn't really give me any guidance as to whether I need to perform additional testing on those negatives at this point.

Bernard Branson, CDC, Session Panelist: I don't know how to address that.

Michele Owen, CDC, Session Panelist: So, I guess that you're really asking what you should do if you the 3rd gen and the supplemental is negative. Is that the question you're asking?

Kimberly Hibbs, The Division of Consolidated Laboratory Services in Virginia: No. If the 3rd gen was negative initially, can I just call it negative apart from the fact that—do I need to have a disclaimer that says that I might be missing acute infections since a lot of what we're talking about is trying to catch all these acute infections? It's not really telling me . . .(not audible)

Bernard Branson, CDC, Session Panelist: I think the advice we've heard from several people is that, indeed, you should issue that result with the disclaimer that says it may not detect really early infections.

Kimberly Hibbs, The Division of Consolidated Laboratory Services in Virginia: Okay. So, it's not really telling me that I need to do further testing on the negatives as long as I'm making that disclaimer?

Bernard Branson, CDC, Session Panelist: Right.

Kimberly Hibbs, The Division of Consolidated Laboratory Services in Virginia: Okay. Thank you.

Bernard Branson, CDC, Session Panelist: Thanks everybody very much for those comments. I want to mention that this was one solicitation of comments. We will end up taking those into account to generate the entire document, and there will be another opportunity when the entire recommendation document is available for comments again. We wanted to get the input. It sounds like we didn't do anything terribly wrong with these recommendations, so I was glad to hear that there wasn't any major objection. I think the most controversial one had to do with what to do after a reactive rapid test. I think Nancy Cornish is going to do "the thing" in terms of talking about anything else other than the recommendations. I do want to thank everyone for their participation, and again, encourage you to let Kama know, Kama Brockmann, if you adopted the new algorithm, and to let us know if you think that you have an application for dried blood spot testing with a 4th generation or 3rd generation assay, because of the interest in moving that along.