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Molecular Diagnostic Panel Testing for Pathogens CAC Meeting Transcript

Meeting Date: January 11, 2021

Jocelyn Fernandez:
Let's begin the meeting.
Welcome to the multi jurisdiction Contractor Advisory Committee (CAC) Meeting for the Molecular Diagnostic Panel Testing for Pathogens. Before we start, I would like to cover a few housekeeping items. All lines will be muted, except for the CAC panelists and Contractor Medical Directors from Noridian Healthcare Solutions and Palmetto. For the panelists, please keep your devices on mute when you are not speaking and remember to unmute your devices before you speak. Each time you speak, we ask that you announce your name, to be clear to the audience on who is speaking. Keep in mind that during the discussion questions, we will limit the discussion to 10 minutes. During your introduction, we kindly ask that you disclose any conflicts of interests that you may or may not have. The chat feature for this meeting should only be used for technical issues. All other issues will not be addressed. This meeting will be recorded, the recording and meeting transcript will be posted to our website. The following slide is the agenda. We will try our best to stick to the times shown.
I will now turn the meeting over to Dr. Anitra Graves.
Dr. Anitra Graves:
Welcome, and thank you for attending the Molecular Diagnostic Testing for Pathogens CAC meeting. My name is Anita Graves. I'm a Medical Director with Noridian and will be acting as the moderator today.
The Contractor Advisory Committee, or CAC today is a multi-jurisdictional Contractor Advisory Committee collaboration between Medicare Administrative Contractors, including Palmetto GBA, CGS, and WPS. We have a very impressive group of subject matter experts on the panel participating today. If you'd be so kind, I'd like to ask each of you to announce yourself and any conflict of issues in order of your appearance on the panelist slide.
Beginning with Dr. Caliendo.
Dr. Angela Caliendo:
Hi, I'm Angie Caliendo. I'm Vice Chair of the Department of Medicine at Alpert Medical School of Brown University. I do sit on a variety of advisory boards for diagnostic companies. I can send you that list. I actually don't know them off the top of my head.
Dr. Anitra Graves:
Thank you. Doctor Gilbert? And we have Doctor Hayden? Doctor Hayden?
Dr. Randall Hayden:
Hi, can you hear me?
Dr. Anitra Graves:
Yes.

Dr. Randall Hayden:
Yeah, Hi. I'm Randy Hayden, Director of Clinical Pathology and Global pathology at Saint Jude Children's Research Hospital, Memphis, Tennessee as well as directing the clinical molecular microbiology labs. I sit on a few advisory boards, and I have a few collaborative research contracts, which I've sent to you in my COI. I don't know if you need me to find it or read out loud, but they're all on there.
Dr. Anitra Graves:
That's sufficient, thank you. Welcome. Dr. May?
Dr. Larissa May:
I'm Dr. Larissa May, I'm a Professor of Emergency Medicine and director of our emergency department outpatient antibiotic stewardship program with special interest in Molecular Diagnostics at UC Davis, Health in Sacramento, California. I too sit on several advisory boards for diagnostic companies and also have research contracts and I submitted those.
Dr. Melissa Miller:
Hi, this is Melissa Miller, I'm at the University of North Carolina School of Medicine, where I direct the clinical microbiology and molecular microbiology labs. I'm also on a number of scientific advisory boards pertinent to the discussion today. In the last 12 months, I have served on Cepheid Luminex molecular diagnostics and Cyagen SABs.
Dr. Christopher Polage:
This is Chris Polage. I'm a Medical Director of Clinical Microbiology laboratory at Duke University Health System. And I basically have similar disclosures to others on this call with nothing actually in the last 12 months, but within the last 2 to 5 years participation in scientific advisory boards for vendors relevant to this call as well as investigator-initiated study funding.
Dr. Anitra Graves:
Thank you. Dr. Rand? You're on mute. Let's work on that, give us a moment. Dr. Rhoades?
Dr. Daniel Rhoades:
Yeah, Dan Rhoades, I am the section head of Microbiology at the Cleveland Clinic. I've had research funding or may have research funding in the near future, for entities, including BD, BioFire, Bio-Rad, Cepheid, ClevelandDx, Luminex, OpGen, Qiagen, & Q-Linea and I'm on the Scientific Advisory Boards for Luminex & Talis Biomedical.
Dr. Anitra Graves:
Thank you and Dr. Wolk?
Dr. Donna Wolk:
I'm Donna Wolk and I'm the Division Chief of Molecular and Microbial Diagnostics and Development at Geisinger Medical Laboratories at Geisinger Health in Pennsylvania. I serve as a member of the CLIAC committee, an advisory committee to the Center for Disease Control and I serve as the infectious disease subcommittee chair for AMP and the evidence-based Laboratory Medicine Practice Guidelines for the American Society of Microbiology. I have research grants relevant to multiplexes in the past three years from BioFire, Luminex and Safeguard Biosciences and I have advisory in the last three years for Q-Linea and Streck, which is not related, but, so, and that's all on my COI.
Dr. Anitra Graves:
Thank you. Dr. Rand? Let me try that again. Still can't hear you. We'll see if we can troubleshoot that, maybe we will get you another link to reconnect to. So, hold on there. We'll work on that as we go

Dr. Randall Hayden:
I did have some trouble connecting and I had to relaunch.
Dr. Anitra Graves:
Yeah, we'll get our, our staff to help him with that. In the meantime. Let me move forward and next slide please and introduce the Contract Advisory Committee purpose. Some of you may have already participated on a committee that a lot of the contractors have conducted in the past. However, as of January 8, 2019, the purpose and makeup of the committee has completely changed. It is no longer, as it was in the past, which is, was typically to discuss the proposed LCD, or local coverage determination policy, and, as of now, the purpose of the CAC meeting is to discuss evidence and literature on a topic. So, we are not, at this point discussing any written or proposed LCD as there is none. We are in a preparatory state and at this point of evaluating the evidence that supports the use and the role of molecular diagnostic testing in the form of panel tests or multiplex tests. So, our CAC members, now, their role, is advisory in nature.
Their comments and opinions around the evidence and literature that assess, assist the CMDs within the MACs to determining whether or not a proposed LCD should even be developed.
This supplements the internal expertise that the MACs have to ensure an unbiased and contemporary consideration of state-of-the-art technology and science. So, we are charged with conducting this process and an evidenced-based framework, and as a result, next slide, I have adopted the PICO process to guide our questioning during this particular panel.
For some of you that may not be aware, the PICO process is a pneumonic and it is a pneumonic that is used in evidence-based practice to frame an answer, a clinical or healthcare related question. This framework is also used to develop literature search strategies and, essentially, this is where we are in our policy development process.
It's essentially a mini systematic review surrounding a particular technology and, in this case, multiplex testing for pathogens. So, the P stands for patients, problem, or population. I is for intervention, or in this case, the test and potentially some other aspects of test procedures and medications, the comparison is typically standard or usual care, and this case, it would be cultures are serologic tests, and the O stands for outcomes.
And so, these are the questions are focused on evaluating what elements we need to insert into our literature search strategy in order to identify that evidence that would be most helpful in establishing the clinical utility and use of molecular multiplex panel testing. Next slide, please.
This other slide is a more deliberate example of the framework.
Next slide.
And it helps introduce the different levels of investigation with respect to a specific test, and where we are, is not phase one. We're assuming analytic validity is solid, and that there is a significant level of technical reliability and diagnostic accuracy. We are beyond the phase two and we are, at this point, evaluating the impact on clinical decision making and health outcomes for multiplex testing and therefore, this is where we're going to focus. We are already assuming that the testing and the panels that are we're discussing, in general, have already met those measures for reasonable and necessary interventions and we're now exploring how we go about using those and whether or not the there is evidence to support the clinical utility for multiplex testing in Medicare beneficiaries.
Next slide, please.

So, the first aspect of the PICO framework that we're going to talk about is the patient population and or setting that is acceptable or appropriate for multiplex testing and our first question. Next slide.
What are the patient populations that benefit from multiplex testing? And I'll open it up to the panel.

Dr. Angela Caliendo:

This is Angie Caliendo, before we get started, can I ask a few clarifying questions?

Dr. Anitra Graves:

Certainly.

Dr. Angela Caliendo:

So, when you talk about patient populations, can we talk about, is these inpatients, outpatients, emergency departments, urgent care? I think of testing in the inpatient side as all falling under the DRG, and maybe I'm mistaken here. So, I just would like to know so I could frame my brain, what exactly, where are we talking about testing at this point. Or are we talking about all of those locations?

Dr. Anitra Graves:

Yes, we're talking about all of them. So, ignoring the impact on whether or not or how these technologies would be paid. What patient population based on your expertise and knowledge of the literature at this point would suggest that they are most appropriate for multiplex testing. Who would you use this technology to evaluate the presence of infection?

Dr. Randall Hayden:

And can you also clarify or remind me or us when you say multiplex testing is that any multiplex testing? Or what delimits the size of the panel that you're worried about, or that we want to talk about?

Dr. Anitra Graves:

That's part of the conversation, and we'll get to that. At this point in the conversation, I'm just trying to ascertain from your expertise. Do we use this, in urgent care? ER? ICU? Where do you think that this type of testing is most helpful?

Dr. Randall Hayden:

So, you would, again, just, you, would, you're including any multiplex testing, whether it's for two targets or 20 targets.

Dr. Anitra Graves:

Exactly.

Dr. Donna Walk:

This is Donna, Go ahead…

Dr. Christopher Polage:

I was just going to clarify what Dr. Hayden was saying.
I think for our group, at least from our perspective, I'm imagining that for us, like influenza and respiratory syncytial virus testing that may have subtyping qualifies as multiplex testing in our terminology and the groups that we think would benefit from that would be broad. Perhaps all patients are many patient populations, whereas, more expansive, multi pathogen panels, perhaps like the Biofire panels that have anywhere from 10 to 20 or more targets might have more limited populations to benefit depending on how you think about it or define it.
So that's why I think Dr. Hayden is asking the question. Can you give us any more guidance?

Dr. Anitra Graves:

Right, well, let's talk about that. Let's first talk about that first panel that you spoke of the respiratory syncytial virus and influenza. There's obviously multiple types of pathogens with those particular

infections on the panel and subtypes. Where would you use those? What patient population would those be important in using and in contrast that or is it the same patient population as those within multiple pathogens, such as the Biofire panel that you spoke of?

Dr. Donna Wolk:

So, I guess, I'd, if we can, by definition, I think the small panel tests are called small panel, the bigger panels are really syndromic testing and any of these panels whether they're sort of small panel or syndromic, I think that we all look at the use of them, and in several buckets. One would be clinical utility, the other is more operational, you know, clinical, operational, financial actionability. So, in the laboratory medicine setting, we're looking obviously first and foremost a clinical utility and then after that, you're looking towards whether these syndromic testing can actually, you know, the lab may spend more money but downstream it's saving antimicrobials and there's downstream either patient related or operational value.

So, that's the clinical utility you want us to talk about today, correct?

Dr. Anitra Graves:

One moment, if you're not speaking, if you could just put your microphone on mute. That way, that will limit that echoing effect.

Dr. Kenneth Rand:

Can you hear me now?

Dr. Anitra Graves:

Yes.

Dr. Kenneth Rand:

Ok.

Dr. Dave Gilbert:

Can you hear me? Just testing? I'm late. This is Dave Gilbert. Can you hear me?

Dr. Anitra Graves:

Yes. Thank you. Yes, we can hear you.

Dr. Dave Gilbert:

So, I've been confused, as I sense my colleagues have been confused, because the previous determination about coverage and so forth was seen based on whether we were, had 3 to 5 elements in the multiplex panel, or 6 to 11 elements or targets or 12 to 25, et cetera and as Donna said, what we really want to know, is, the result going to affect patient care in a positive way? And it seems like you're asking for generalities. And the generalities are tough. You know, is this a 80-year-old person in an outpatient setting with a bronchitis? Or is this a child with a bronchitis? Is the 80-year-old admitted to the, excuse me. Is the 80-year-old admitted to the hospital? And if admitted to the hospital, is the patient in critical care unit or on a general nursing unit? What are the comorbidities of the patient? et cetera, et cetera? So, we're down to pre-test probability. We're down to clinical judgement and I'm really perplexed as to how we can help you cover all of those variables, if you will, I guess confounders is the popular verbiage.

Dr. Anitra Graves:

I agree with your, so, we're actually attempting to transcend this limitation of, a panel covering 3 to 5, 5 to 7, 7 to 10. I'm not sure that that we can support based on the literature that the specific numbers on a panel indicate the clinical utility. So, for example, we won't be talking about children because we're talking about the Medicare population. So that certainly is the context that I'd like to limit our

discussions about. However, we talked about, as Dr. Wolk refer to the small panels that have just maybe 1 or 2 viruses with several subtypes. I would have the expectation that that type of panel would have more clinical utility in an outpatient urgent care setting as opposed to an ICU and the syndromic testing with the, you know, multiple pathogens both bacterial viral would be most, my expectation, would be that would be more of a complicated or complex care setting such as an inpatient our ICU. So, based on your use of these panels is that what you would expect there used to be most beneficial to the Medicare patient population? Or should we never see syndromic testing in a, for example, outpatient clinic, family practice clinics? Would that be accurate?

Dr. Larissa May:

Just wanted to say a little, like, the other perspective of things is, what do we mean by clinical utility? Right? Because there are a lot of studies that suggest a theoretical benefit, perhaps, assuming that the clinicians are actually going to take action, and I think we have really limited evidence in many cases, that that actually happens. Even if, theoretically, it could be useful, you know, the implementation of these tests is often lacking because, you know, the turnaround takes so long, or the clinicians don't see it, or the clinicians don't trust the results. So, I think it would be helpful for me to think about what you mean by clinical utility.

Dr. Anitra Graves:

[unrecognizable] What the population is. So, we're going to get to the clinical utility aspect of that. But for this question, we're only asking who is the most appropriate patient to have this testing done as opposed to a simple sputum culture or serologic tests. Who would you expect this to be performed in?

Dr. Randall Hayden:

But you're, you're asking for, for bright lines, and it's more of a Venn diagram, right? Because almost anyone can benefit from a small panel and many of the patients that could benefit from a big panel benefit from a small panel. Whether or not we had these panels clinicians would order between 2 and 15 assays on a given patient. So, putting them into panels, merely consolidates what the clinical lab is doing in many cases and I think it's not really possible to draw non overlapping lines of populations that would benefit from one panel or another.

Dr. Dave Gilbert: I agree with Randall, and you could come up with any myriad as scenarios. So, I've got a 25-year-old, who's got a possible community acquired pneumonia during influenza season. I have the Liat point of care test available for respiratory syncytial virus and influenza and the patient mentions that at home Grandpa's there and Grandpa is undergoing chemotherapy for cancer and is immunocompromised and maybe I say, hey, I don't really want to know just about the two viruses, I want to know about adeno virus and meta pnemo virus, and even rhinovirus, et cetera. Maybe I should order the expanded panel. Oh my! But Medicare won't cover that would be $500-600 blah blah blah. I mean, [unrecognizable] we're into a corner, and then, one more thing, and I'll promise to be quiet. Angie, I will be quiet. Anyway, I lost my train of thought, I'm sorry. Oh, I know what it was. I know what it was. You keep asking for literature, for clinical effectiveness, cost effectiveness, and so forth, and it's time, money and people. We all have the experience with antibiotic stewardship of having face-to-face feedback with the MD provider for the patient and they're almost uniformly incredibly receptive to that, et cetera, et cetera. But until we fully implement stewardship programs, it’s going to be hard to get the kind of data that Larissa was suggesting we all want to see we all feel that the hypothesis is valid, that if you give the clinicians hard data of what virus, what bacteria are there is potential pathogens, they'll

behave appropriately. We're just not geared up for it. It's sort of like the start of the immunizations for COVID-19. It's a lot of rough spots to get through.

Dr. Donna Wolk:

I think if you could get to the quick of the matter, any, the populations are based on, not necessarily the traditional medical populations. Although, in some cases, they are, but they are based on the fact that you can, you can have a syndromic test, that, that creates actionability. So, the emergency room setting, the ICU, the as many are saying, if you have the pipeline that that, communicates and creates actionability in your organization, then almost any of these multiplex panels, given the right population, whether that's ICU or sepsis patients, or GI patients in the emergency room where they have to decide, you know, to send them home or admit them. I think that the populations are just about anybody, but that anybody in the framework of are you going to have them come into the emergency room and waste money on an ED visit, or are you going to keep them in the clinic and be able to care for them there so that you avoid an ED visit, or you avoid an ICU visit? Those are really the things where syndromic testing are important when you need a fast answer to the most common things that could prevent either a downstream sequela for the patient that might not be good. Or, a downstream sequela for the organization that may be costly and I don't know if that frames it, but I don't, I no longer look at these as old, young, immunocompromised, not immunocompromised populations anymore. I look at them as where can we have added value for the patient and the organization.

Dr. Larissa May:

I think the only challenge is we can't really separate this from diagnostic stewardship in general. You know, I think of GI panels in the emergency department, I mean, there's not a lot of evidence that, for non-immunocompromised, like healthy patients, the emergency department, that even stool cultures have much value. So, so, talking about the sense of multiplex panels when really the recommendation might be, we're not supposed to be testing in this population at all. You know, as an ED clinician, that's, you know, that's kind of what I see happening in the emergency department, specifically, granted, I don't have experience in other settings, but in the ED and urgent care setting. I think there needs to be a discussion also, like, should in, do we really need any of this testing and then what is the added value of doing the molecular testing and then what is the added value of doing syndromic testing?

Dr. Angela Caliendo:

So, I would, I would also comment that we have to think about standard of care for respiratory viruses culture and serology are absolutely no longer the standard of care. So, it doesn't matter where the patient is or who the patient is. Those two modalities are absolutely off the table and so as Donna and several others have said, you need to keep that in mind. It's a matter of what a center can do with the information or what a physician can do with the information, and we can talk about what did we say, small panels versus syndromic panels. But, under no circumstances, should we be talking about anything other than molecular testing for respiratory viruses. GI, is a different story. GI, as Larissa said, it's more of, OK, you have acute diarrheal syndrome. You shouldn't be tested. There's really good algorithms out there if your symptoms are greater than seven days old, or if you have a fever, if you have bloody diarrhea, if you're septic, if you're immunocompromised, you can break it out, and, and you have a better understanding of what patient population to use it on, and so, think about standard of care for molecular, is absolutely the standard of care. Fast-forward over to meningitis, well, for viruses it's absolutely the standard of care. It, some still serology, but not so much for bacteria. So, there's so many, we need to sort out what we're talking about. We would want to first talk about respiratory pathogens, then we can

move the GI, then we can move to blood, but they're very different conversations, as Larissa and Donna just said, between respiratory syndromic panels and GI syndromic panels.

Dr. Randall Hayden: And then legislating that action by trying to constrain the size of the multiplex panel is, in some ways, sort of a fallacy in the sense that, you know it's, again, the practice of medicine that needs to be informed and so, at least where I am, and they're going to order all the things they want whether or not they're in one panel, and so you know, you know so fine, we're only allowed to do a three plex panel and then we end up having to do six of those in order to get everything that everyone ordered. So, you know, or are we say we're not getting reimbursed so, we don't have the test and we end up spending even more money sending it to a reference lab? And so, by constraining, the size of testing panel, is not, what is going to modify standard of care.

Dr. Gabriel Bien-Willner:

[Unrecognizable]

Do you mind, Dr. Hayden, if I ask a follow-up question to that?

So I think one thing that we'd like to establish revaluate in the discussions is around that very point you just made, which is around restricting the size of the panel, to what, could be described as some arbitrary number of pathogens or analytes. I mean, one thing we'd like to do is, revisit whether that should even be the approach for how we consider, what is a necessary, or reasonable and necessary test. Would you, would you say, would your opinion be, that it's more important to look at the right pathogens rather than the number of pathogens?

Dr. Randall Hayden

Well, if we knew the right pathogen to look at, of course, it would be great. Just to, you know, go for the jugular so to speak. But you know, when multiple different organisms or infections present very, very similar and overlapping clinical pictures, you know, think about it from the terms of culture. In culture, when you send a culture, you expect to culture everything that grows, and the breadth of the molecular panel does improve the chances of finding the etiology.

[unrecognizable]

Dr. Gabriel Bien-Willner:

If I could maybe reestablish the question, for any, thinking about it like a differential diagnosis,

OK, somebody comes in with respiratory or GI or neuro symptoms. Is there, for example, certain pathogens that should always be in your differential that should be considered to be a component of such panels? Or do you believe it's more appropriate to just say, you know, there's a number of pathogens that should be looked at that, that's more important than, than the specific pathogens that are included in a panel. And again, I just wanted to re-iterate, that when we say panel, we mean multi analyte testing and we, at this point, don't have a distinction between a small panel or syndromic panel, and we're not even sure that that distinction should be drawn, and really, we want you guys to tell us whether that such a distinction should be drawn.

Dr. Larissa May: [unrecognizable]

Dr. Melissa Miller:

This Melissa Miller, I just going to go back to what, Angie's sorry, Larissa. These are different conversations for these different panels. I wouldn't have the same conversation for a GI panel as I would, a meningitis panel or a skin and soft tissue panel on and on and on. There is no way for us to answer this question when the question simply states multiplex testing. I'm not comfortable with that,

there's not data to support that. I think we have to talk about it in terms of the actual syndrome we're talking about.

Dr. Larissa May:

Melissa, I was just going to say exactly the same thing, and I was going to say, you know, there for some conditions. I mean, you never want to send a test just to make a diagnosis. Or, you know, if you're not going to do anything with the result, then, of course, it makes no sense to send it and so, you'd think of things we have very good evidence for like acute bronchitis in a, you know, in an outpatient, like, why would you, why would you ever just look for which virus might be causing it? And, and, you know, so that I think, I think there is that. And then, I agree with you. I don't think we can have these conversations unless they're set. We need to talk about the specific syndrome that we're talking about. [unrecognizable]

Dr. Gabriel Bien-Willner:

Let me follow that up again because I think what we're interested here is not what's true in respiratory disease, those same exact, those same exact conditions are true in GI. What we tried to establish is an underlying principle or philosophical framework that may be true in all settings, or only true in some setting, and if it's only true in some settings, and we can focus on those specific settings. So, if what we're hearing, for example, is that in respiratory, symptomatic patient panels can be necessary, is that, is that, are those same conditions true in other situations? Or is it only true in respiratory?

Dr. Dave Gilbert: Can you say that again, you broke up?

Dr. Gabriel Bien-Willner:

Sure. The idea that panels for multi analyte testing, which is done with molecular methodologies is now the standard of care in respiratory testing and should be considered in respiratory testing. Is that framework, is that idea, [unrecognizable] I think there's just feedback, please mute if you're not actively responding. Is the idea that a multi analyte test, a multi pathogen test would also be necessary in other patients and in other situations? Not necessarily that the specific same pathogens apply, but that the idea may apply.

Dr. Dave Gilbert:

Yes, yes, yes, yes, so there's potentially actionable data and it's individualistic, you're trying to generalize all of those confounders that I was trying to present earlier. If I have a patient with bronchitis, who's 20 years old, a college student, and sure its most probably viral, but it could be mycoplasma, it could be chlamydia, it could be even on the rare side Bordetella or something of that nature and even Legionella. So, under, depending on the full clinical scenario, if there was a multiplex panel available that could distinguish the virus from those atypical bacteria, a well-meaning and appropriately motivated physician, might order that test. But he's not going to order the test if the patient is going to be stuck with a bill for a thousand dollars.

Dr. Larissa May:

Well, also, I think, you know, as Angie pointed out, what is the standard of care?

So, one could argue the standard of care for a 20-year-old outpatient urgent care is not, with a presumed viral respiratory tract infection, or even a presumed community acquired pneumonia, would not be to send a molecular diagnostics and multiplex panel in that, in that patient.

Dr. Christopher Polage:

[unrecognizable] Since we're considering Medicare population, why are we hypothesizing about children and young people to be focused only on Medicare beneficiary age group?

Dr. Anitra Graves:
Yes, that's exactly the scenario that we need to be focusing on, and therefore, I think what we have already done through this conversation has identified multiple patient populations, those patient populations, and with a specific attention as we're talking about Medicare beneficiaries. Medicare beneficiaries with respiratory symptoms it sounds like, Medicare beneficiaries with gastrointestinal symptoms it sounds like, Medicare beneficiary, that may have systemic infection systems such as Sepsis. It sounds like those are populations of patients that the panel testing, or multiplex testing may be appropriate and as we're speaking of the outpatient setting, would it be your expectation to test a beneficiary that has no comorbidities and coming in with a sinusitis, is that the correct patient to do this type of testing? Or rather would it be in somebody that would have comorbidities whereby they are more vulnerable and potentially have more complicated treatment plan? Tell me a little bit about how you might delineate. Does everybody have with respiratory symptoms benefit from this multiplex testing?
Dr. Angela Caliendo:
Remember you've defined multiplex as not small versus syndromic. So, every one of those patients you described would benefit from a multiplex test. Some of them might benefit from something with flu and RSV in it and others may benefit from a very large panel. But since we, we have lumped them all into one bucket, yes, they're all going to benefit from that because it's the standard of care.
Dr. Dave Gilbert:
If you have a patient in the, be a Medicare patient with COPD having an acute exacerbation of their chronic bronchitis, and they've got to infiltrate at least one that's being suspect to infiltrate on their chest x-ray they're going to be admitted to the hospital. Do my colleagues agree that if available, if available, the patient would potentially benefit from a multiplex panel? That would be part of the DRG of course.
Dr. Larissa May:
Are we talking about upper respiratory or lower respiratory tract?
Dr. Dave Gilbert:
Lower
Dr. Christopher Polage:
Lower, because the patient had an infiltrate [unrecognizable] they would benefit, there's no question. Obviously, you could make arguments about empiric treatment and so on and so forth. But, yes, they would it would definitely benefit. I don't think you can say just because somebody has respiratory symptoms, unfortunately, that you always benefit. So, for example, the guy who comes in short of breath with chest pain and gets, and I'll skip ahead, gets the CT scan looking for embolus and has an embolus, obviously does not need a respiratory panel and so on. So, yeah, it's, it's complicated. Unfortunately.
Dr. Angela Caliendo: But I would say the reverse is also true, just because I'm a normal, healthy, 80-year-old, doesn't mean I don't need to be tested. I come into the emergency room with shortness of breath, even though I don't have any comorbidities other than I'm 80, I still need to be tested, and this is the way to diagnose respiratory infections.
[Unrecognizable]
Dr. Larissa May: As an ED clinician, I would argue that that's still not standard of care, and an 80-year-old coming in with respiratory symptoms, most of whom are going to be just, I guess, I would say

from the ED perspective, most patients that are getting discharged with the current implementation of the tests would probably not benefit unless there were special circumstances.
[Unrecognizable]
That that's not true.
Dr. Angela Caliendo: You have to diagnose influenza in an 80-year-old.
Dr. Larissa May:
You know what, I'm going with the full panel again; I'm also getting confused.
Dr. Angela Caliendo:
No, no, see that's the problem. We were talking about everything in one bucket.
Dr. Larrisa May:
I agree with you.
Dr. Angela Caliendo:
Making this conversation so challenging.
[unrecognizable]
Dr. Gabriel Bien-Willner:
So, to make it a little less challenging, if, Dr. Caliendo, I'd love to have your feedback on this. Sorry, Anitra, to just jump in on. You're talking about syndromic testing and small panel testing. We're happy to distinguish those two things, but what is a clear differential or a clear distinction between those things? Is there an absolute difference between one and the other? And what would make, what would make that up?
Dr. Angela Caliendo:
I mean, yes, there I can give you situations where I could be perfectly happy, just testing for influenza or influenza and RSV and I can give you situations where I would absolutely want the large panel, like, immunocompromised patients, people that have to be hospitalized. But, there's no sharp line, and that's what's making this challenging for us, is there's no clear separation that says in this situation, absolutely, in this situation, not and that's where I think we're struggling a little bit. [unrecognizable]
Dr. Gabriel Bien-Willner:
At this point, where we are in a conversation, it makes sense to just consider both of them as the same. Because in both situations you're still looking at multi analyte testing. Maybe a little bit later in the conversation be more specific as to why one and not the other. You know, from our perspective, what is the difference between saying, on the test side, between a syndromic test and a panel test? Is it just a number of pathogens? Are we happy with an arbitrary distinction of the number that will differentiate a small panel from a large one? Those are questions that we may, we may get to. I think the first thing is consider panels as a group that would include both small panels and large panels, and then we can maybe sub stratify further.
Dr. Dave Gilbert:
While back to Dr. May in the emergency room. So, I've got my COPD patient, who's got pneumonia, is going to be admitted to the hospital, and we've just done and coincidentally just published our results with some 500 patients, and one third of them had viral etiology or a potential viral pathogen present. One third had potential bacterial pathogens, the usual suspects plus a bunch of Moraxella and haemophiles influenza and one third had both, including some with staph aureus and influenza combined. So, it seems to me that I would want to benefit the patient and reduce the insecurity of the providers by getting the large panel on such a patient.

Now some hospitals have taken a step approach and started out with just the limited, mainly viral panel, and then if that's negative reflex to the larger panel. Larissa, what do you think of that?

Dr. Larissa May:

I mean, I don't know. I've reframed how I'm thinking about this to 65 and up now. So, I think that is a different patient population. I still don't think that most ED clinicians have access to this technology in such a way that, you know, it's going to come back in real time to make it actionable in the ED. So, I still think that, you know, it's more beneficial to the inpatient team in general than it is to antibiotic stewardship or delaying antibiotics or starting the right antibiotic or impacting empiric therapy in the ED setting. But, again, my experience is really just ED. So that's. [unrecognizable]

Dr. Dave Gilbert:

That's, that's absolutely fair, and I should have said, we, I cheated a little bit in my comments, and that we had turnaround times of one to two hours. And it, we also had procalcitonin levels that were influencing judgement as well.

Dr. Christopher Polage:

I think one point I'd like to make to clarify this, and this circles back to Anitra, your framing of the scenario a few minutes ago in terms of a patient with respiratory symptoms. I think we need to clarify that there's got to be some threshold clinical suspicion for infection or for viral infection, and I realize that's not perfect, but so if we clearly suspect an acute infection, whether it's on top of comorbidities or what have you, I think the standard of care would be to rule out influence as a treatable cause in a 65-year-old or older patient.

But if we think we've got somebody with a CHF, CHF exacerbation or, or some kind of underlying other thing that they come in, for typically, or even with an MI, or something like that, and we have little, or no clinical suspicion for a viral infection, they may still have respiratory symptoms, we're heading in a different direction. So, I still think that really it has to do with, we could have patients that we don't think need any testing at all. We think we have patients where they definitely need testing, at least for treatable things, where, where detecting a pathogen like influenza would automatically send us down a pathway of trying to treat to reduce risk of complications. And then I do think that there's patient populations, like Angie said earlier, where we absolutely would want to test even more broadly and I'm sorry if I'm stuck in the three to five versus syndromic panel kind of paradigm, but I would say all three buckets are conceivable.

Dr. Randall Hayden

It seems like Larissa's point and other points earlier that the question early here is about medical practice and when you're going to look for infectious diseases, and if, if you find someone that you're going to try and test for infectious diseases, almost invariably multiplex panels are going to come into play as a standard of care now. So, if you're trying to figure out whether people are looking for infectious diseases, in the right patients, Again, that becomes a very broad question that seems like it's very difficult to get at in the context of a panel like this.

Dr. Larissa May:

Well I think it's hard because we don't even send sputum cultures at all, especially in patients being discharged. We just don't do sputum in the emergency departments, I would not say that that is standard of care, which is why I was focused on the inpatient populations, at least for LRTI. For, you know, for upper respiratory infections then you would argue that it might not be as beneficial, right? If the patient has a presumed viral infection to know what that viral etiology is other than influenza.

Dr. Randall Hayden
That's my point. I mean, it's just whether you're going to send a test. If you're not going to send a test fine. If you are going to send a test that's likely then that being a multiplex PCR.
Dr. Larissa May:
Right, I agree, I agree with you there.
Dr. Christopher Polage:
It's like, is a test indicated at all? If a test is indicated, what things might you treat if you detected it, or what things maybe, you know, would have clinical relevance. Dr. Gilbert pointed out having different individuals at home, or things like that, perhaps infection prevention implications, even if you couldn't treat.
Dr. Donna Wolk:
I was going to say, I think we're looking at this from an individual, patient perspective and I think we're forgetting the overarching benefits of value-based care, and population health. I mean, in that, in some of the settings that you've described, the 80-some-year-old. You may not need to know that they have RSV, although, you know, we see in the winter that 40% of our adults have RSV and would have been falsely treated for influenza. But the same symptoms of ILI if we didn't know they had RSV. But now send that 80-year-old home with RSV and not knowing it, to her great grandson who was just born and now you've got a kid in the ICU. So, I think, you know, we could talk about Medicare population and we can talk about infection prevention or intervention or preventing the spread of influenza and other things. We don't just use multiplex testing for an individual patient in our organization because we're very focused on that population health and value-based care proposition, which you know, is guideline driven in our organization and in some cases, we have some publication to show that those are useful.
I mean, but to globally, just say how you would use them and to Larissa's point or Dr. Gilbert's, if you're doing multiplex testing and you don't have your results to the ED within an hour, an hour and a half, then you shouldn't be doing it for them, but you know you should, they're not going to be able to use it, so the speed, all of this was driven upon the speed for actionability and prevention of illness, in other populations, or sequela.
You know, if you've got MRSA and a flu, you should be watching that patient. Because if you don't, they could have necrotizing pneumonia and cost the health care organizations across the globe a lot of money. So, I think there's the individual decision making, but I think there's above and beyond. There's a lot more that needs to go into it from a population health, a value-based care perspective.
Dr. Christopher Polage:
Well, where would reimbursement decisions really make a difference in this, in getting testing done in the right patient populations? So, one of those populations is the population that comes to the ED but gets discharged. Because their test is not covered under DRG, they're going to get a bill, and that's a very, they are symptomatic, so the testing may be justified on that basis but they're not sick enough to go in the hospital and yet they could end up with, you know, a multi thousand-dollar bill, of which the laboratory testing is part of the culprit.
Dr. Donna Wolk:
I mean, two cents on the dollar, right? So, we're down from three cents on the dollar to laboratory being two cents on the dollar. So, if you're an insurance company, and you're looking at try to saving money, can, I mean, should I approve the adeno virus, on a on somebody, on some kid that's already had a flu test because I can prevent a CSF tap or an adult for that matter? Yeah. I mean, there, there's, there's other

decisions besides, the unique individual diagnosis that could be saving money for organizations around the country, if people didn't have to pay out of pocket to do that. Like, we don't know the full utility or financial benefit of doing this because providers across the US cannot make their decisions outside of the regulatory or insurance-based scenario. So, when you look at what's published in the literature, it's only the tip of the iceberg of what can be, if, if these things could be ordered outside of a research setting.

Dr. Angela Caliendo:

You know, I know that you don't consider cost, and you don't want to talk about cost. But if these tests were reimbursed at a much more appropriate level, this conversation wouldn't be so difficult. Because the cost wouldn't be so high. So, if you truly reimburse these panels, the really high number of panels like 200 to 250 bucks. It would change everything. Right? It would change the bill the patient got it, it would change the cost to Medicare, it would change everything. So that's just. I'll throw that out. I know it's not what you want to talk about, never is, I get it. But it's actually drives a lot of how these tests are looked at and the issues that we face on the clinical side about billing and what the cost is left to the patient. So just going to throw it out to be out there.

Dr. Gabriel Bien-Willner:

Can I follow up on that, Doctor Caliendo? So, let's set aside the idea that there is [unrecognizable]. Sorry, there's feedback. Set aside the idea that we were talking about data outcomes data for a multi analyte test. When you say that things will be different? What, why do you say that? What kind of information, what kind of evidence are you, are you talking about?

Dr. Angela Caliendo:

So, I think we all, you heard at least four different people make a comment about a patient getting a thousand-dollar bill, right? And that happens when they come into the ED and don't get admitted or when they're in the doctor's office. So, that's what we're talking about, and I've lived through this from the laboratory perspective, and now from the clinical perspective. So, I think if, if we weren't generating such outrageous bills for people, that it would, the value of this test would be, could be framed differently, that's all I'm trying to say. Is a you know, it's not often that I sit here and say, how much is a laboratory test really worth? But a lot of this conversation that this is included in a lot of the conversation, particularly, again, in the respiratory panel, where it's, it has clinical utility in any number of settings, GI, we, we've talked already a little bit about more limited settings where that GI panel is useful. Blood cultures, again, more limited, right? Not a lot outpatients get LPs that need the panel testing for their lumbar puncture, right? That's usually done in someone who's coming into the hospital or is already in the hospital. So, respiratory pathogens are interesting and a little bit different because there's not a clinical situation or location that you can come up with where it's not appropriate because, as we said earlier, it's a standard of care.

Dr. Daniel Rhoades

This is Dan Roads. I just want to chime in. I think one of the challenging things that I think other people are saying, is that these tests have that have qualitative value, or there is some clinical benefit to them. But value, meaning, benefit over cost, often ways in these discussions is often challenging to divorce the cost or the charge from, from the approach from, you know, our thoughts about this, sometimes, I consciously kind of divorce it in my mind by saying, if this test was free, is there any clinical benefit? And so, I think for, for outpatients I know we're not talking about kids, but for outpatients you could apply this to adults if somebody comes in and they want a Z pack and the doctor or provider says,

I think this is a viral infection, and then can prove it with the multiplex panel, that would be valuable clinically, because it reinforces that decision of the provider and helps improve the perceived care that the patient is receiving, confirming that it is a viral infection. You know, there could still be a bacterial infection, but, you know, if the private provider's assessment is that there's not a secondary bacterial infection, that provides some value. Now, is it worth a thousand dollars? Probably not. Is it worth $100? Maybe. Is it worth $10? Probably. But, you know, all these have you know clinical benefit, but it's hard to divorce it on how many dollars' worth of benefit.

Dr. Dave Gilbert:

To reinforce what you're saying, Dr. Rhoades, I'm such an ancient Doctor now, I can remember when the rapid strep test was introduced, and it was 40 or $50 for a rapid strep test. But it was a game changer, once implemented, because of obviously, withholding antibiotics when the rapid strep test was negative, and now, what's the cost of a rapid strep test? Last time I checked it was $2 and it's an, it's a standard of care, right? I mean, we would not want to see anybody evaluated for a strep throat without having a rapid strep test plus minus a backup culture, et cetera, et cetera, et cetera.

Dr. Anitra Graves:

Well, I'm glad we entered this area of the conversation, and I'm just going to move this, panel forward. We're going to get to the intervention aspect of our questions, and this goes to or speaks to some of what we were just talking about this particular question. Which is, what is the advantage of multiplex panels versus a la carte tests might be the challenges of cost and improved availability of the smaller panel tests that were referred to in the past, benefit the Medicare patient population as opposed to just the large syndromic panel test? So, is there a benefit to a la carte tests in terms of cost versus the multiplex panels or, or not?

Dr. Daniel Rhoades

Well, in the sense that a lower cost for an institution translates into a lower charge. There would be a benefit. I need to come back to reimbursement. But, in general, the cost of the larger panels is greater to the institution. So, therefore, for the outpatients who get stuck with those bills, they get a higher bill. So, yeah.

Dr. Larissa May:

I think from the literature perspective, oh, sorry. I was just going to say for [unrecognizable] perspective that I think there is evidence that for certain patient populations and forgive me, I think one of these was a VA study, but others may have included other younger populations that, you know, that the real benefit to doing the syndromic testing was really just for influenza and other maybe RSV, but not, you know, like, does it help the clinician to know that an elderly patient has rhinovirus? Because then you still, you know, you're not going to do anything differently and also you haven't proven or disproven that there is a bacterial coinfection.

Dr. Melissa Miller:

So, for a different perspective, for let's say, not the respiratory, this is Melissa Miller, like a meningitis panel, for example. You know, I'm at a large academic medical center and many of these tests I can do on my own without a panel. However, we have a lot of community hospitals in our system. They don't have a standalone HSV. They don't have a standalone enterovirus. They don't have strep pneumonia antigen testing. So, I think there is cost benefit to doing the panels and certain situations and this is something I've come to appreciate. Particularly in the community setting, especially when they're not going to be doing the testing in-house if it is ordered, but it will be sent to our reference laboratory.

Dr. Donna Wolk:
And anytime you can this, Donna, anytime you can prevent disruption of a microbiome in an adult or an elderly person. So, maybe the benefit is not to say that they have, you know, meta pneumo virus, or Bordetella, maybe the benefit is to, sorry, virus go back to virus, maybe the benefit is that that person's not leaving the ED with a Z pack that's going to disrupt their microbiome. I mean, some, the truth is C. difficile, and all the sequela of all the overuse of antibiotics impacts these patients' health. Maybe not at the moment that you're diagnosing them, but two, three weeks later, they go back to a nursing home and then the antimicrobial disruption on their microbiome makes them more susceptible. These things are very difficult to weed out. But, again, I think that the discussion needs to be more of a, of a whole person analysis rather than at the point of care and contact and having that fast answer for the top 80, 90 pathogens in that syndromic panel is beneficial because somebody walks away knowing what they have and can protect their family or can avoid antibiotics and even antivirals. I mean, if this pandemic was influenza and we weren't allowing influenza documentation, the, the antiviral stores would be depleted. I think, you know, now, we're not talking about that in general terms, but the concept is the same. We have to look at not just what is diagnosed but what is prevented by having the diagnosis.
Dr. Daniel Rhoades
You know, it's also, to Melissa's quite a bit of a matter democratization and what's available to people. I mean, you know, so we're going to find a way to do these tests, many of us in our practice settings. and they're simply not going to be available to some people if they're not available in a multiplex panel and, and further the cost of the healthcare system will be higher, because they'll either ship them out, they won't do them and won't get an answer. Or, in our cases, we'll do them at a much greater cost to the laboratory, and to the health care system, because we'll end up doing ten tests instead of one.
Dr. Larissa May:
I just want to put the ED stewardship perspective in place here because I think, you know, we can do as many tests, I completely agree. You know, like that what we're trying to do is diagnose viral infections, but I'm not sure that these tests, like, are, like really do that, at least in an ED perspective and I'm not sure they're going to stop clinicians even if they're diagnosed with a virus and we have some limited evidence that or contradictory evidence in the literature that, you know, these tests may not, having the result even in real-time may or may not have an impact on what the clinician does and I would also argue from the ED perspective that that we don't need these tests. Like, for example, to reduce antibiotic prescribing for acute bronchitis. Like we know we have other methods to be successful on that without a diagnostic test. So, I just, sort of from the ED outpatient perspective again, I'm not sure of the value of syndromic testing for most of these patients who have don't have underlying comorbidities or special circumstances.
Dr. Dave Gilbert:
So the laboratory expense for the inpatient comes out of the DRGs and Ferric Fang and colleagues at the University of Washington did a cost analysis test which, I'm sure my laboratory folks on this call are well aware of, where he compared the cost of the GI panel to the cost of the al a carte menu, where the same tests were ordered separately, and they had to go to multiple different parts of the laboratory, et cetera, et cetera and by memory, it seems like it was cheaper to do the panel than to do the separate tests. I am sure that we did the same thing with our pneumonia study and came up with essentially the same kind of result because we didn't have to use so many different parts of the laboratory to do separate

PCRs for the pneumococcus and staph aureus and the viral panel in the urine antigen, et cetera, et cetera, et cetera, that was in a pneumonia population.
Then the other thing, to get to Donna's point about the whole person, and the whole institution, the DRGs are a big deal to the C-suite, to the hospital administrators, and so length of stay becomes a big deal with Angie shaking her head because she lives through this probably every day. So, if we can get to a diagnosis for the inpatients quicker and determine that they don't need a higher level of care, (i.e. IV, antibiotics, et cetera, et cetera) we can get that patient in and out of the hospital in a day. Reduction in length of stay is a big, important, economic driver of decisions to give us enough time, money, and people to do effective antibiotic stewardship.

Dr. Anitra Graves:

Well, this is a fascinating conversation. And it dovetails into the next question, which is, how do you select what multiplex panels to purchase for your lab? What are the specifications that are important to you? This is this is a perspective that is very unique to some of you on the panel, because I'm interested in finding out do you discern or distinguish between certain panels because of what organisms are on the panel, even for a series of panels, multiplex panels, all with respiratory viruses, or maybe some with both respiratory and bacterial, and so forth. As with gastrointestinal organism, what about panels will cause you to purchase them for your lab to use?

Dr. Melissa Miller:

This is Melissa, again, I definitely have picked panels based on what is on the panel, but also the ability to hide targets on the panel. So, for example, I don't want C. diff on a GI pathogen panel. So, we specifically wanted a GI pathogen panel that maybe wasn't as broad and even if it has C. diff, but I have the ability to hide C. diff on the panel. So, throughout our implementation of multiplex panels, we have often looked at the targets that are on it for the patient population that we serve. In terms of other smaller entities and our health care system, it's not quite as straightforward. A lot of times, they're looking at what instrumentation they have in their lab already and what panels are available to put on that instrument. For example, they may only have, you know, instrument X, so they're going to do the Biofire panel if that for us, just try not to say a name, but there it went, so they are going to do the panels associated with whatever instrument they have. So, it's certainly not uniformed that people look at the panels and the targets, and the size.
[unrecognizable]

Dr. Christopher Polage:

When we implemented our GI panel, for example, the breadth of the targets on the panel made a huge difference because we were able to eliminate the stool bench in effect, and we were able to eliminate a lot of other testing in the laboratory, which streamlined our operations. For us, a lot of this boils down to the impact of not having enough techs in the lab, the paths on us so that we have to streamline our operations, and, unfortunately, it's, it's can be made on based, based on decisions like, factors like that.

Dr. Donna Wolk:

Also, the complexity of the tests, like, these tests are, meant to be actionable. So if you can't perform them, maybe with the exception of the stool panel, which is still probably O.K. for first and second shift, but in general, if it's not [unrecognizable] complexity, or you don't have the staff 24/7, 365 to perform these things, that weighs into our decision as well. Like, Melissa was saying, with, what do you have that's available for the community hospitals, but, also, even if we are in a bigger center, we have, the importance of it, is that it's not just used on people for day shift testing. So, if it's important enough to be

actionable, then the complexity, as well as the breadth and the depth, and obviously the accuracy are important.

Dr. Christopher Polage:

I'd like to ask the group, are there examples on other panels besides the GI panel, where individuals have made decisions perhaps, to limit reporting of certain pathogens? Or to not select certain panels, because pathogens that you didn't want were on that panel? Or is that really only the case with GI panels and C. diff?

Unidentified:

I think Bordetella owns [unrecognizable]. So, I think that's not clinical [unrecognizable] questionable.

Unidentified: I have an example, it's not exactly what you're asking, but, for example, we don't run gram negative rods and positive blood cultures on the BCID, because there's almost no actionable result we could get whether it's Pseudomonas or E.coli, you're still going to cover them to know what sensitivities are. But that's not exactly the same, it's not exactly a suppressant, we're doing a global suppression based on a gram stain rather than suppression of the result.

Dr. Melissa Miller:

We have definitely suppressed targets, and sometimes they're rare targets that we're just not able to validate. That's one reason we have suppress targets. So, a false positive, more likely going to be true, then a true positive. We've also suppressed antigen C. diff before, but we have other examples adeno virus on a GI panel, we suppress again, because we have a large transplant population and just detecting 40 and 41 it's not enough for us and we don't want to put out misinformation and providers think, oh, they're adeno negative, and we miss a disseminated virus infection. So, there's a lot of thought put behind the targets and a multiplex panel that we report. That being said, we're at an academic medical center and I know that's not true for the community hospitals in our health system.

Dr. Christopher Polage:

The reason I asked the question, we've got some of these examples, as well, I mean, I was trying to take the pulse of the group, but I wish there was a way, in a nuanced way to get at this with this discussion. Because I think if I had one perhaps concern with some of the larger syndromic panels, it has to do with the degree to which some of the panels have crossed patient populations and crossed clinical syndromes and I think there can even be false positives that are not clinically significant and that these can occur sometimes with surprising frequency and so it's a, I think it's become more complicated. Like, like, for example, to Angie's point from earlier, we use respiratory panel right now as a pure respiratory virus panel and then we attempt to do other things for atypical bacteria, et cetera.

Dr. Gabriel Bien-Willner:

Can you illustrate a little bit more of the potential harm of having too many pathogens or the wrong pathogens on the panel?

Dr. Dave Gilbert:

Well, I'll ask Angie to comment, because Kim and Angie and others had the wonderful review article on the subjects that we're discussing and the question is with the broader panels we detect, a lot of organisms be they bacteria or virus that might be colonizing and that can be a potential downside in terms of the uninitiated providers and well, Angie found the bug I must have to treat it. So, Angie, how are we going to separate, or should we intercalate into this discussion something that differentiates colonization from invasion?

Dr. Angela Caliendo:
Yeah, that's going to be, that's a good point. I think it's most obvious with the GI panel, right? There's things in that panel in some of the panels that we wouldn't have chosen and I think that's best managed by the laboratory deciding what to report and what not to report, to keep from misleading people. But it gets complicated because I have seen symptomatic infections in immunocompromised hosts with GI pathogens that you wouldn't have thought, and they're symptomatic and you finally decide to treat them, and they actually have responded. In fact, a couple of times we have seen that, but I think that needs to be managed locally at the lab, and it's mainly GI, I think, although there are, there are issues with the larger meningitis panel. It's interesting, you guys were talking about things you don't report. We don't allow the broad panel until you've had a standalone HSV an enterovirus test, because the ones in the panel are not as sensitive, and we don't want it to be the, you know, we're afraid we're going to miss something. So, it's not, these panels are not perfect, is how I would answer that, both from a sensitivity and specificity perspective and a lot of that needs to be managed by the people on the call that run these laboratories and understand what, what they should suppress, and what they should let go.
I don't know that that really influences, and I don't think we could begin to manage the nuances of colonization versus infection.
Dr. Randall Hayden
Nor can you I mean, it's, it's not like you wouldn't do culture because there's colonization, you have the skills to either interpret or provide guidance. So you know we don't…
Dr. Angela Caliendo:
That's a really important point, Randy, you know, one of the questions here was about, something about the net worth. I wrote it down. I can't find it right now, but that's no different than culture. We culture things all the time, that grows something that we have to put in a clinical context and decide whether or not we're going to act on it. All of a sudden, it's NAT testing and we set this ridiculously different standard. Respiratory culture is really good example of, you know, it's like, OK, what's it mean, so we don't want to set a different standard for NAT, just because it's NAT, right. This is called a clinical decision making, so, it's a very good point, Randy.
Dr. Christopher Polage:
The only caveat I would make to that, Angie, and it's far from perfect, that with traditional respiratory cultures, which I'm not trying to defend, but, but we, we do attempt to set thresholds for when we report it. And certainly, many laboratories have practices, where you, you don't report bugs in, in any concentration, when normal flora is present. We have specimen adequacy checks when we because we recognize these things can be colonizers, and this is distinct from respiratory panels where everything is qualitative, and we have ratcheted up the sensitivity of the panel. I think we're starting to see some exciting changes with, with pneumonia panels, where we're starting to try and distinguish things and sort of fiddle with this. But I do think there's some methodological differences, is, I guess, all I'm pointing out.
Dr. Angela Caliendo:
I think that's a fair comment, although I will say in my laboratory days trying to standardize how each tech worked up a respiratory culture was not always the easiest thing, we spent our time on. But I think it's a point well taken.
Dr. Christopher Polage:
Totally.

Unidentified:
Yeah, you're certainly correct that if it's buried in the normal flora, or if it's in lower concept of potential pathogens and lower concentration than the normal flora, we do ignore it and we don't work it up. But what if that were MTB? I always, that thought nags at me. MTB is always a pathogen, but pseudomonas low concentrations, never is? I don't know. Again, it just shows the complexity that you're alluding to both in culture and it's going to be mirrored and already is mirrored in the NAT testing in the pneumonia panel where you have semi quantitation and that you know that adds another degree of complexity in terms of interpreting the significance of these findings.
Dr. Anitra Graves:
Actually, this is actually the, literally, the next question, in the next section, under outcomes, but I want to first stop and find out if I need to stop here, we have a break scheduled, but I'm going to leave it up to the panel. Do you want to just drive forward, and you break out when you need to, or do you want to take a break here as scheduled to 3:30?
Dr. Donna Wolk:
I have to step out and come back, but I will come back. This is Donna.
Dr. Angela Caliendo:
I think we just go; people come and go. You know, I think most of us have told you when we had to leave. so, we can just continue to talk.
Dr. Anitra Graves:
Let's drive to that next question. Can I get the slide 22 Outcomes Facilitated by Multiplex Testing and that question that you just started to talk about was the question that I had. Do multiplex testing results indicate the presence of infection? One of the concerns that I've seen in the literature, that a positive test may or may not be indicative of that. How are these tests in determining whether or not there is a presence of infection is and is there a difference with respect to what we're talking about? That sounds like you've already alluded to this gastrointestinal organisms versus respiratory organisms versus those in the systemic presentation.
Dr. Dave Gilbert:
Well, there's a huge difference between a sterile body fluid versus one that has a normal flora. So, pathogen in the spinal fluid is a lot different than a pathogen in the respiratory tract or GI tract.
Dr. Donna Wolk:
And this is Donna. I guess. I also want to point out that our dogmas are also based on the ability of our previous laboratory tests to make certain distinctions. For instance, you know, in the eighties, when we were doing cell culture, we thought that you'd really only have one virus and when the multiplex panels come out there's multiple viruses and now there's some evidence to show that having multiple viruses even linked with bacteria at times is a bad prognosis, and can have higher consequences and may have to be attended to in a different way. So, I think it's a sliding scale on, you know, the fact that we're basing our comparison on less than optimal findings at times. I mean when, when new evidence does, you know, eventually emerge. So, it, it, these decisions really depend on whether the predicate is a molecular test as in the respiratory viruses. Like Angie was saying you want to do the most sensitive test or whether the predicate is something that we don't know what to do with, with culture anyway. We've, we've avoided, if we don't know what to do with it in culture, we've avoided doing it molecularly. But, on the other hand, I think, that also has to come into play that, yes, there are times when cultures need to be interpreted and there are times when molecular syndromic panels need to be interpreted. But, that's,

that's the presence of medicine, that's up to the provider and the laboratory to figure out. So, I don't necessarily think we can say, because some of these are more sensitive, that they're not valuable, because, in some cases, they are, and vice versa. Sometimes they are a little bit too sensitive, or, I don't want to say it that way, they don't have the markers of the, the rest of the normal flora as a comparator. That's where it's most difficult to interpret whether or not that presence is indicated because you don't have a cellular marker for adequacy of specimen type, and you don't have an indicator of the other normal flora.

Unidentified:

I would also argue that if the panel at least if you want to do a panel and that panel never picks up contaminants that the panel probably isn't large enough. In other words, it's not going to be sensitive enough if it's got 100% positive predictive value for every panel member, then, you know, you're probably missing some things. And I would just like another panel.

Unidentified:

Like the old adage, a surgeon who operates for appendicitis and has 100% accuracy, he's missing a bunch.

Dr. Daniel Rhoades

This is Dan Rhodes. I think it's analogous to culture. The results need to be interpreted, as others have said.

You know, as an example, there might be a few colonies of strep pneumonia or haemophilus influenzae in a respiratory culture, is the is the organism really there? Yes, it's there. Is it causing infection? Well, you know, the interpretation of those results, meaning the results being the organism's there, the interpretation is whether or not it's causing an infection is challenging and it's challenging whether you are culturing, it's challenging if you are multiplexing. And you know this, I mean, the converse of this question is if the multiplex testing results are negative, does that mean there's not an infection? You know, that's also challenging. For example, cryptococcus in the multiplex meningitis panel is thought to be less sensitive than cryptococcal antigen testing. So, if it's positive, it's very helpful. If it's negative, it doesn't absolutely rule it out.

Dr. Anitra Graves:

This is helpful based in the context of where we are, right now with COVID, right? When we started off taking care of these patients, there was not a confidence in the test results. And therefore, many centers, including my own, waited until there was a better-quality test to even start testing potential patients for that illness and so, do you believe that with more use of these types of panels? Well, let me ask you differently, is that competence in the, results of these panels? Do providers, physicians, and other practitioners, use this information directly in treating these patients? Or do they use that in as an adjunct with cultures at this time?

Dr. Melissa Miller:

Again, I think it's very panel dependent, it's patient dependent, it's epidemiologic dependent, right? You don't treat a test result, you treat a patient. And so, there are too many variables in here to answer the question that she just pose, because it really depends on the patient who is in front of you. For example, you know, well, the example is going to use, probably not a good example, but, you know, there will be situations where a positive result on a meningitis panel, for example, maybe definitively what's going on in a patient and another patient requires more testing to be done to determine the context of that. So, my, personally, I think it's impossible to answer your question.

Dr. Larissa May: I think one of the things that we have to think about just from a clinical perspective, you know, as clinicians, I think the clinicians are always asking what they think are performance characteristics. They ask about sensitivity and specificity and then they forget that these, or they're not able to interpret these molecular tests or tests, you know? For example, for viral RNA, they're not test for the disease, right? So that happens a lot with, with COVID, right? What they don't take into account, what we don't [unrecognizable] is the prevalence and what clinicians really care about, which is negative and positive predictive value. And so just because something is more sensitive, but you know if the prevalence is low or high then it's you know, there's going to be different considerations and interpretation, and you we don't do a great job, I think, educating clinicians about that.

Dr. Dave Gilbert:

I agree with Larissa. So, patient who's been on oral antibiotics gets admitted to the hospital has signs of meningitis, the culture's negative, but the PCR multiplex panel is positive for a partially treated bacterial meningitis, be it the [unrecognizable] pneumococcus whatever, and so that's different than the patient with pneumonia who produce, first of all, half of our pneumonia patients can't even produce the sputum, but those that are awake enough to produce a sputum we find all sorts of bacteria as well as viruses and we have an adjudication committee, if you will, between the primary care provider, the ID consultant, the stewardship committee, et cetera, et cetera that has to put together imperfect data to show whether or to gather evidence one way or the other whether this is an invasive bacteria or pure virus or combination of the two and so, it's the clinical scenario, the laboratory results, the biomarkers, et cetera. So, this is an, to emphasize what others have said, this question is impossible to answer.

Dr. Anitra Graves:

Well, we'll segway right over to our next question, then and the next question is somewhat related. Is there evidence to show that multiplex panel panels impact medical decision making? I have been in review of some of the literature, and there is some conflict on this. There was a study that was looking at the respiratory panels and this, the question was whether or not the results of the respiratory panel would change the decision a physician might have in sending a patient out with antibiotics and what this particular study found was that, if there was an influenza diagnosis then it certainly impacted the decision making. However, if there wasn't influenza that was positive, whether or not only a virus showed up didn't matter, the patient was sent home with antibiotics. So, can you speak to whether or not and what level of impact that we've primarily been talking about respiratory, so, it sounds like this is where this is primarily used in, but are there are there episodes of care whereby these multiplex panels actually impact medical decision making, I guess, in my mind, one example would be the systemic infections, but what are your thoughts on it?

Dr. Angela Caliendo:

Well, yeah, study that you quote is the VA study that someone mentioned earlier. There's also other studies out there that show that it is used and some of those studies you gave us, some of them are actually in guidelines that if we decide to move forward with any of this, those clinical guidelines should be included in references because they do drive how we think and one of them for sure is immunocompromised host. And you know, that's all over guidelines from IDSA transplant association and immunocompromised people should have a very broad approach to how we do diagnostics and they may not come out specifically and say, you should use these broad multiplex panels because some of the guidelines are a little older than the panels. But yes, there are, there are definitely studies that you can

find where it didn't change people's practice and there are studies that you can find work that change people's practice.
[unrecognizable] So, this is what Melissa said, this is what Melissa said in the very beginning, can we break this out into specific situations so that we can have more focused conversations?

Dr. Melissa Miller:

I was going to say, even where there is an impact, you know, I mean, Dr. Polage and I did a study, like it didn't really show the impact we would have wanted either. I mean, you need a large number of patients to demonstrate benefit. I mean, you're talking about like 500 patients to demonstrate, you know, benefit in a study for example, and it's not clear if you're outside of that study, with all the ideal turnaround time and the stewardship and everything that you're doing, you know, doesn't really change decision making. I would argue that the tests should be adjuncts. You know that they don't supplant good antibiotic stewardship and particularly in the outpatient setting, there isn't a lot of antibiotic stewardship, like focused antibiotic stewardship that's happening. Which is, again, why I think it makes a lot more sense to me in patient populations.

Dr. Anitra Graves:

Great. And then we'll just go to the next question because I do think we'll spend some time on this one, Question 10. What are the net health outcomes when using multiplex testing, as opposed to cultures and serologic testing? and I do want to make sure that we think about these net health outcomes in a broad on a broad basis. So not just whether or not someone gets better faster, or we get antibiotics more quickly, and that may be one of the outcomes. But what can we think about with respect to health outcomes that the multiplex testing has an advantage of over cultures and one of them have already been spoken to with respect to viruses.

Unidentified:

So, you're speaking, in some cases, about comparing to tests that are completely out of the standard of care, now. So, I mean, I'm not even sure how to address this in the context of something like you know, you're asking for respiratory viruses, where no one does cultures, for the most part is serologic testing. So, how would you even frame the question, let alone the answer and viruses and CSF? You know, who here does cultures for that? I am not sure, I'm not sure the meaning of the question in that respect.

Dr. Anitra Graves:

Well, then what about gastrointestinal infections? What are the health outcomes and certainly stool cultures are things that still providers do? What is the advantage of multiplex testing in that?
[unrecognizable]

Dr. Christopher Polage:

I was going to say, one of the studies that came out of our institution show that with the GI panel and the docs getting it resolved within three hours or something like that of submitting as to what they thought was a stool culture, it had significant downstream testing effects and fewer radiographic studies, fewer CT scans, I think fewer ultrasounds and less antibiotics. I mean, it reduced the diagnostic uncertainty and it was definitely an outcome for the health for the hospital and the institution as well.

Dr. Angela Caliendo:

And that the manuscript was not included in our packet.

Dr. Christopher Polage:

Pardon?

Dr. Angela Caliendo:
And, you know, I would just say, you know, if again, you look at what several people have told you, is that these molecular tests are now used instead of bacterial culture. So, there's total value there. I get a result that day instead of three days later, O.K.? So, there's value to molecular there. Is, you know, do I have enough data to show you what happens downstream? No. But you're giving me a result. And Melissa wrote a really nice, commentary on this with the ASM group saying that, you know, when you give someone the result faster and it's accurate and they can make a diagnosis, we have to appreciate that that's value, even if we don't know all the downstream repercussions of that value. To disregard the ability to give someone a rapid, accurate result is not appropriate. You should not be disregarding that, there's value there. But certainly, in stool, and then in viruses, I'll go back to the immunocompromised host. They're the ones that are getting sick with things that the rest of us don't get sick with. They're the ones that have more than one pathogen and we have to know it and do something about it. So, yes, there are populations where this is of value and again, I would take you back to the article you did give us from the Mayo Clinic with a very good algorithm on how to test for gastroenteritis and so, yes, there's value. Can I tell you people are living longer? Less people are dying? No. But there's clearly diagnostic value to using these tests.
Dr. Anitra Graves:
Now are there any limitations based on the type of institution? In other words, or community hospitals that have maybe a less than 150 beds, do they have the same capabilities of performing these types of testing and having the results as timely as those more reference labs and academic institutions?
Dr. Angela Caliendo:
I think that Melissa made that the comment earlier about the actual appreciating the value of even more of these highly multiplex tests because they're so easy to do, and it gives them access to testing they otherwise wouldn't do, like stool cultures, right? Now they can do them.
Dr. Melissa Miller:
Yeah, I agree. We're even seeing now with respiratory panel testing us. You know many of these now have SARS could be in them which brings up additional discussion. I'm sure we don't necessarily need to get into today, but their turnaround times are faster than our turnaround times because they're testing is more focused than all the testing that we're doing in our labs. So, they routinely get an hour or less turnaround time on their panels where even though it only takes that long, we're not able to get that same turnaround time. So, I think it's better in the smaller hospitals.
Dr. Anitra Graves:
So that's interesting. So, actually, this health outcome would add and would include better access for Medicare beneficiaries to diagnostic test, diagnostic testing that would be sensitive enough and accurate enough to optimize their management, so that, that's, that's interesting and that's an important thing to consider. What other health outcomes, some of the others that were reported in some of the literature I was looking at, was even things such as isolation in the hospital and being able to get patients out of isolation for various organisms that we now isolate patients for, do you think that's a value?
Dr. Dave Gilbert:
Sure, why not?

Dr. Christopher Polage:
Sure. We do it. That's our standard of care, you know, everybody gets a respiratory panel with respiratory symptoms. To get them out of respiratory isolation. The RSV and other respiratory pathogens can spread within the hospital, maybe not this year, but they'll be back.
Dr. Angela Caliendo:
And, you know, there, as I said earlier, there's some respiratory data out there on reducing length of stay and reducing ancillary testing. I think that's very important for blood cultures. You didn't have Banerjee study there where it didn't show necessarily a change in length of stay. But it did show people getting on the right antibiotic more quickly and spending less time treating contaminants. As Donna Wolk mentioned earlier, you're just eliminating the unnecessary exposure to antibiotics. So, there's all sorts of value out there and outcomes out there, it's in pieces and parts, it's not as beautiful as we would all like it, because the studies are so difficult to do. You know, you're asking about outcomes, like as if it's tying your shoes, these are extremely difficult expensive clinical studies to do. So, we have to take the best data that we have, some of that is published and some of it is our own clinical experiences of what it's doing to the access to testing that otherwise wouldn't be there.
Dr. Anitra Graves:
Any other comments on this issue?
Dr. Gabriel Bien-Willner:
Anitra, I would kind of like to follow up with the train of thought that has been discussed here. I think this last conversation, I think, was really helpful. We talked about, again, I want to clarify when we're talking about net health outcomes, we mean very much like what Dr. Caliendo was referring to it's not strictly a patient to live longer or get better faster, can simply be [unrecognizable].
Dr. Anitra Graves:
Can we all put our microphones on mute so that we can get that the echoing down? Thank you.
Dr. Gabriel Bien-Willner:
Yeah, so, the question, we discussed a few things, which was clear discussion of where it's standard of care to do these, that have demonstrated improved health outcomes, even if they're hard to measure, as well as, as long as you can define them. We talked about respiratory infections, we talked about meningitis, we talked about GI, reducing at least, diagnostic uncertainty and potentially reducing delays in immunocompromised patients. I guess what I wanted to ask, or, are there other situations outside of respiratory, neurologic, and GI, where these are usually applied? And then, alternately, the opposite question, which is, are there are occasions where people use these kinds of panel tests? And you believe that there really isn't a use case for them, but there are people who do them?
Dr. Angela Caliendo:
So, the data I just talked to you about was in blood cultures, the Banerjee Study. So, there is data that, using, in certain situations, using these rapid tests to confirm a blood culture is going to be important. You know, we talked when we were preparing for this call, and one of the conversations that came up was this whole thing about nail clippings, and what a waste it was. But, just to give you a little different perspective, as long as it is required that a definitive diagnosis of toenail fungus has to be made by the laboratory before anyone will cover the treatment, you have to ask yourself, does it always have to be culture? O.K.? So even though there's no data out there, and we all said, oh, my God, we have no data for nail, what I do know, is that the antifungal necessary for treating nail fungus is not covered without a culture. And even though any primary care doctor, podiatrists, and many other providers out there, can

look at your toes and tell if it's a fungal infection. So, as long as we have cray, cray, things like that going on, then, can you argue that, if I don't want a culture instead, I could do a rapid molecular? I don't know, I'm just I'm just giving you a different perspective than the fact that none of us has seen a whole lot of data on toenail fungus molecular testing. But, you know, some of the other payment model decisions that are made drive the craziness of what's done.

Dr. Gabriel Bien-Willner:

I'd like to personally thank you for addressing the toenail fungus. That is basically, why we threw it in there.

Dr. Dave Gilbert:

Well, the other thought that's going through my head, I agree with, really all the comments that the panelists have come up with. Is that somebody said tip of the iceberg and I think of the general issues that we've discussed are the tip of the iceberg. Looking towards the future with next generation sequencing, with meta genomics. We're going to increasingly find application of molecular diagnostics into other clinical syndromes, the infected prosthetic joints. These STD panels, I even saw a panel, I think, if my memory serves was from colleagues in Europe, on patients with pharyngitis and they must have had like 20 different targets for what was rule out strep pharyngitis panel, if you will. So, I applaud the organization for trying to get us to give you some general guidelines, but you've got a tough task ahead of you for all the reasons it's been expressed.

Dr. Anitra Graves:

I appreciate you bringing up the STD that, if there's one aspect of the literature that's fairly clear is the outcomes surrounding the molecular testing for STDs as it pertains to not only to the patient but to public health. So that's another example that we didn't discuss explicitly but is also part of the conversation. I wanted to just thank you so much. This panel has been extraordinarily informative for us, and again, the intent is of this discussion today is to provide the elements of the data that we can then use to look for the literature to support or to address whether or not it supports, it is immaterial at this stage. But to look for the evidence that's there, and, as someone has said in the earlier part of this conversation, not all of what we do is proven by randomized controlled trials and that's just very clear. So, the path to coverage determination doesn't require that. However, it does require preponderance of evidence that we have available, which includes those expertise and standard practice that you have all alluded to. So, we will take these responses back. I'm going to be sending you a link to rate some of the answers that you have, or rank some of the answers that you have provided us. They'll give us a little bit more, just another angle of a way to evaluate the literature, and then I hope to come back with some specific areas, targeted areas, and I think some of you recommended that as our approach so that we spend we have attention to the respiratory system in particular, we have attention to gastrointestinal applications, we have attention to CNS and the systemic systems, and we can have a conversation about skin and nails if you'd like. But I do think that that's the right approach and, again, I want to thank you all for your very enthusiastic participation. And I hope you continue on the committee as we move forward in this investigation.

So, thank you very much for your help with this, and I think we can close there, unless Gabe do you have some other comments.

Dr. Dave Gilbert:

No, I'm good.

Dr. Gabriel Bien-Willner:
For me, I would just say again thank you all. Thank you Anitra for putting this together. I think, you know, ultimately, our goal here is to try to understand the space as well as we can. What we would like to do is to make policy that reflects when services are reasonable and necessary, so that we pay for services that are reasonable and necessary. The last thing we want to do is to create conditions that [unrecognizable] that are useful to physicians and that we don't know for sure, until we hear from you and the experts, and so, thank you again for your comments.
Dr. Anitra Graves:
All right. Well, I'll give you some time back for your day. Thank you again for participating and we'll close the meeting. Thank you.