

Gideon: Maybe if we could have people start, take their seats for session 4 we'll start in about two minutes. I'll call you guys up. Okay great so we're in the home stretch bottom on the 9th inning. In the previous session you guys we were drilling down very much on the Nano scale, we were talking about orthogonal methods, contrived specimens, limits of detections.

Now we're going to zoom way out to 30,000 ft. for the session 4. Which is titled Accelerating Liquid Biopsy Applications to Improve Patient Care. We have a great lineup of stakeholder presentations, we have [Sumimasa Nagai 01:49:19] from the PMDA in Japan, Andrea Faris from Longevity to represent the patient voice. Gary Kilov from the NCI and the FNIH. As well as a doctor and a lawyer, a mother's dream Dr. Robert [McDonald 01:49:37] from [inaudible 01:49:39].

Before we kick off with Dr. Nagai I just wanted to frame the issues. There's a lot of interests from all different stakeholders in these exciting technologies, billions of dollars in investment into these technologies. It's important to hear first of all how are we going to value these new technologies, how are we going to get them reimbursed? We heard a lot earlier today about standards and transparency. Are there any efforts we can do potentially public private partnerships to promote standards?

From a patient's perspectives, patients they're less, Andrea can correct me if I'm wrong, but less interesting in some of the technical details but they want to make sure that the test is reliable. It's accurate and it leads to a safe and effective therapy. Then of course in the drug development and diagnostic development space there's international development issues to consider as we heard earlier today. Dr. Nagai will help us frame at least from the Japanese perspective what the outlook is there.

From a drug development standpoint, we have a long history of using potential surrogate endpoints like pathologic CR and breast cancer, HIV viral load also there have been investigations into a minimal residual disease in various hematologic malignancies. These take large scale efforts, well designed randomized control trials met analysis.

It's important to ask questions now, it may be early but it's very important to ask now what we can do from a public private partnership perspective to embed these technologies into the existing trials going forward so that we can use them to inform drug decision making down the line. Following the talks, we'll have a great panel discussion, we'll have Dr. Beaver who's a breast oncologist at the FDA, Dr. [Girish Pucha 01:52:06] from [Moviex 01:52:10] and Geoff Oxnard from the Dana Farber as well. With that I will call up Dr. Nagai from the PMDA.

Dr. Nagai: Thank you very much for giving me a great opportunity. I'd like to talk about Japanese regulatory perspective very briefly. Combined diagnostic working group in PMDA was founded four years ago and this is one of the projects across multi offices in PMDA. As activity of this working group this notification approval application for individual combined diagnostics and corresponding therapeutic products was released three years ago.

Main contents of this document are to specify definition of combined diagnostics and to

recommend simultaneous submission, marketing and authorization applications of combined diagnostic and corresponding drug. This is a Japanese definition of combined diagnostics and these are very similar to US definition of combined diagnostics. Identify better responder and identify high risk patient and finally it's to monitoring those schedule.

In addition, we released technical guidance on development of individual combined diagnostics and corresponding therapeutic products three years ago. Main contents of this document are how we should evaluate data from bio-marker negative patients in clinical trials and how we should evaluate [inaudible 01:54:19] by analysis on bio-markers and how we should evaluate concordant studies. Our concept in this document a little similar to FDA's developed guidance on co-development published last week.

PMDA workshop on combined diagnostics was held two years ago. More than 400 parties met from academia, industries and regulatory agencies. This workshop concluded that stakeholders must cooperate to deal with two issues. One is what type or what amount of clinical data necessary for approval of [inaudible 01:55:04] combined diagnostics and number two is how to regulated multiple diagnostics such as next generation sequencing.

Very recently they is a notice to applicants for marketing authorization of DNA sequence and next generation sequence utilized for genetic testing systems was released. Basic concept of this notification indicates handling of DNA sequencers, manufactured and marketed for the purpose of diagnosing, treating or preventing disease in according to this Japanese law. This [inaudible 01:55:51] based diagnostic system in Japan. Temporary DNA preparation agent such as [pimoset 01:56:01] classified as [inaudible 01:56:03] diagnostics and DNA sequencer with sequencing sample preparatory agent is classified as medical device. Software for bio-informatics analysis is also classified as medical device in japan.

Handling of genetic variance of [inaudible 01:56:23] and clinical significant. They are two points and so also detecting genetic variance of uncertain clinical significance is not eligible for marketing authorization and providing the result as the different information is acceptable only when the physician considers it necessary. However, in such circumstances caution must be exercised so that physicians are appropriately informed that genetic variance which have not been approved have uncertain clinical significance and unknown analytic validity.

This is a main difference from the US and Japan. Regarding clinical equivalence this concept is now being discussed in a research group composed of academia industry and regulators including me. This is applicable to combined diagnostics that detect or measure the same bio-marker and correspond to the same track and they utilize for patients with the same disease as the difference combined diagnostics.

These combined diagnostics may utilize different methods of detection measurement such as PCR or next genetic sequencing and fish and different object substances such as DNA, RNA protein and different specimen types FFB and Plasma. Liquid biopsies are applicable to this document from the difference combined diagnostics. Placed within

this document but this document is on the other discussion so not yet fixed and not yet published but very late development phase.

Retrospective studies usually cannot collect data on efficacy and safety about the corresponding [inaudible 01:58:20] patients are judged to be bio-marker positive by new combined diagnostics and bio-marker negative by difference combined diagnostics. This [inaudible 01:58:20] corporation data cannot be obtained from the already conducted trials enrolling only bio-marker positive patients in bio-difference combined diagnostics. In principle clinical samples of patients treated with the corresponding drug should be collected prospectively in a new clinical trial in order to [inaudible 01:58:33] clinical parity.

This is a very conservative concept so we are discussing there may be cases where conducting new prospect with clinical study is not necessary for evaluation of clinical validity. Examples described in the following slides are now under discussion. Good concordance in analytical performance was demonstrated using samples of patients with the same disease as the indication of the corresponding drug in each case described below it's one of potential cases were prospect with clinical study is not necessary.

Otherwise new combined diagnosis utilizes same components related to methods of detection or measurement same methods, same object substance and same specimen types and has some same purposes as difference combined diagnostics. In other words, this case is complete from ...

... in company of diagnosis cases. The number says the new diagnostics utilizes different components or methods but same specimen types and date, same point mutation with addition as a different scope of diagnostics. For example, [inaudible 00:00:20] mutation detected by PC Allen NextGen [inaudible 00:00:24]. For in such cases, it is not too difficult to discuss or examine this code and cases. [inaudible 00:00:37] this code and cases in this case.

On the other hand, this is not applicable to cases where [inaudible 00:00:49] needs to be specified such as the application or detect protein by immunohistochemistry. In such cases, it is very difficult or very important to examine clinical impact of this code and cases, this code and samples. We consider that this is not applicable to detecting point mutation cases on the [inaudible 00:01:24] in such potential cases we have prospect clinical studies not necessary.

In addition, we feel that cases we have very high on [inaudible 00:01:37] was demonstrated between different company and new company diagnostics. In such cases, also potential cases where prospect of critical study is not necessary because in such cases, it is impractical to correct critical samples with this company results between difference and new company diagnostics even if a new prospect to clinical studies conducted it because that come preparations are very rare and few in cases where very high unethical confidence data was demonstrated.

Regarding liquid biopsies, we are discussing that the critical utility of company diagnoses

for plasma samples may have to be taken to account in some cases where two more tissue biopsies are not feasible at high risk. The difference between company diagnostics for plasma samples and for tissue samples is evaluated on a case by case basis because in very high unethical confidence data was demonstrated very rarely in the liquid biopsies. Confidence is at very high force negative rates of liquid biopsies because of small amount of tumor set of reading in it.

This concept is too strict when regarding liquid biopsies. We consider that such in discussion regarding liquid biopsies. Today's my talk is partially described by "Nature Biotechnology" in publication. I would appreciate it if you could read inside this publication. Thank you very much for your attention.

Gideon: Next, we'll have Andrea Ferris, the CEO of LUNGEvity.

Andrea: Hi. I actually don't have a lot of slides. I don't have a lot of data, and I don't have words that patient advocates need to Google. Although, today, I got to say when I started going to these medical meetings, I looked up every other word. Alicia [Seacrestin 00:04:03] has been a very fine teacher as have you [get on 00:04:06], to helping me understand a lot of these things. Today, I only had to Google too so I think I'm making progress.

Thank you for having me here today. It's really exciting to listen to all of the presentations and to learn about liquid biopsies. I mean, who wouldn't want these to work? As Gideon mentioned, I am from LUNGEvity. We are a patient advocate group representing lung cancer patients. We also fund millions of dollars of research in biomarker based translational research both for early detection and therapeutic. This is a topic that is very close to my heart.

Just a few years ago, there were many, many doubters that we would ever be able to figure out how one's own immune system could target cancer and to fight it. Now, it's one of the hottest areas of development. Now, we're looking at how bodily fluids can be used to both diagnosis, monitor and manage the disease which is just pretty amazing.

One thing that I think we need to remember when we think, when we listen to all these things, we have heard a lot about all the cases. We've heard a lot about all the subjects. We've heard a lot about all the samples, but really what we're talking about are all the people. All of these people here, who are represented are lung cancer patients. The youngest one over there in the corner there, Elizabeth, she was diagnosed when she was pregnant with her first child. She now celebrated her second wedding anniversary and is watching her child grow.

Actually, all the people on this page are here and are doing well because of either targeted therapy or immunotherapy. For them, biopsy, especially liquid biopsy, holds huge promise. Patients, they are willing to undergo and endure a lot of invasive procedures, the complications, the inconveniences of what these biopsies hold all for the promise of what the right therapy can do for them.

With that, I think that we we need to make sure that the tests that we perform are not

only manufactured well, but as Gideon said, return reliable, sensitive and specific results that can lead to the right decisions. Making informed decisions based on bad information can lead to really bad outcomes. I don't think anybody needs to ... You don't need to say that. Today we heard a number of questions: what tests should we use? When should we use them? What do the results mean and how will they guide patient care?

I was reading one of the recent ASCO posts, I actually do read it, and Dr. [Schiltsky 00:06:33] is in the audience, I saw him here but he made a statement in it about liquid biopsies which really resonated with me. "Just because a test can be done, it doesn't mean it should be done. And it doesn't mean that it's informative." Thank you, Dr. Schiltsky for that. I think it pertains to a lot of the conversation here today, as well, as we are going through this.

From a patient perspective, and a patient advocate perspective particularly, there are a number of things we need to address. What are the minimum standards that a test should meet and how do we know if they're clinically accurate? How do we create transparency in the test results? Girish, I think you mentioned that before, and I know we have been on working groups to talk about it also but not all tests are created equal. How does a patient or a clinician, particularly those in the community setting where 80% of the lung cancer population are treated, how do they know which tests to use?

To that end, how do we ensure that clinicians in a community setting know how to interpret the results of these tests? They're very complicated. Geoff, you talked about that before. It's an art, not a science. Well, hopefully it will be a science, but there's so much art involved with it that patients can really be damaged and harmed if put on the wrong therapy because their doctor doesn't know how to read the result.

How do we educate patients about what liquid biopsies realistically can and cannot do? I think that's also a very important thing, and that's incumbent on us patient advocates to help with that as well as the physicians.

I think one thing that Dr. Susan Love once said also really resonates with me is, "The only difference between a doctor and a patient," and I think can make the argument for the only difference between anyone in this room and a patient, "is a diagnosis." When developing these liquid biopsies and getting caught up in the exuberance and excitement of it, let's make sure that we're also applying really systematic approaches to analyzing them to make sure that what comes to market is reliable and accurate and good for the patient. Thank you.

Gideon: Okay, Gary. You're up.

Gary: This is the advance, right?

Gideon: Yeah.

Gary: Gideon, thank you. Pasi and Reena, it's a great meeting. In one day, you've accomplished an awful lot. They had asked me to talk about multisector collaborations.

It's my pleasure to be at the NCI, a great institution. The last three directors have asked me to chair the cancer research committee of the foundation for the NIH which is all about multisector collaboration. That's how we ... You can't really do this work, or you can do it a lot more effectively if you have as many people involved as you can.

This slide really talks about the partners in our public-private partnerships who we've collected ten or so projects in the last three or four years that are on-going. Some have all the partners, some have a few with the master protocol. A lot of that work was done that created iSpy2 and LungMap. It's cutting edge and our FDA colleagues have been superior in terms of helping with strategy. Of course, they are looking for evidence based regulatory policy.

Each of these stakeholders have sort of a work scope, sort of a mandate, why they go to work. We respect all of it, and all of it has a role to play. All of them can be of value. You can't pick up a newspaper whether its the Moonshot or whatever it is where you knock down silos, everybody has to work together. We do this everyday trying to figure out the place where we can work together. A lot of times, finding the pre-competitive space can be challenging. Sometimes, it's fairly easy to find.

To liquid biopsies, we've been thinking for a while. Certainly, this slide really derives from realizing that you need tissue to make a diagnosis. We realize that imaging can be complimentary, and then the red type is really where the strength is of those assays. You see the complementary of the way that these two assays can and has been the standard for clinical decision making, but we really think at the bottom, the blood serum plasma markers are addressing a lot of the limitations. You see in the two columns in the black type where there is a limitation, and you say, "Can a liquid biopsy help solve that?" We think with some more work, that is the case.

Louie Diaz, this is his slide. It's great; it sort of demonstrates the CTDNA. I think the DNA fragments half-life is two hours. I think that's important to keep in mind as we try to do this. This meeting has been associated with a lot of great data and science. So, I won't belabor this slide, but very low amount of CTDNA can be mixed with a lot of normal sorts of real challenge. We've heard about it. Of course, the sources ... You've got high turn over tissues that are normal skin, GI tract, bone and the tumor DNA has to compete with that. Of course, other tissues are seeding the blood and plasma with these DNAs.

This slide we like from Dan Haver and Victor Vakulesko, and I think it's complementary to the other sides and across the top you see basically the liquid biopsy and the different uses that it has in terms of refractory disease, metastatic. There are different context of use questions and each of them are important. Often, you go for the first, for the easiest.

On the circulating tumor cells, we convened in the foundation about five years ago, all of the folks that were developing circulating tumor cell assays. There were over thirty. At the end of it, we could not determine what the best study or manufacturer should be; so, we defaulted and wrote a white paper with our twenty or so colleagues that are listed. This sort of lays out ... I would recommend that. It's not so dated even four years ago.

As we looked at this and wanting to ask the clinical utility question, we also determined that we should look at the evidence. And, it is really quite clear that it's very difficult to get clinical utility because you don't have access to a lot of the data that you really need to have. It's a subject for ongoing interest in clinical utility as a challenge for all of us. In general, it's going to come from patients that are being treated everyday in standard care settings.

As we thought more about CTCs, we did decide this last year to fund one study specifically for two reasons that this study kind of came to the top. The first thing is it's in a metastatic setting where you have a surgical oncologist that's actually looking at where he's going to biopsy. So, he can pull touch preps from the colon and also from metastatic sites. At the same time, a liquid biopsy can be taken before the surgery and after.

Basically, if you want to prove the concordance of what you get out of tissues, from what you get out of the blood, this had this look about it. Also, secondly, looking at single cell analysis, you heard Howard Shure earlier with the EAV7. It's a great story for prostate. What's making that work is you're finding a rare event and clone a population. So, we think that single cell analysis is absolutely going to be needed as you follow disease and clones within clones grow and you have to find these rare events.

Peter Kunis, the PI on this, he's got a great group of surgical oncologists. We are there with the FDA colleagues and our NCI colleagues and our great pharmaceutical sponsorship from Aviam and IG SanQ and Lilly. This is truly a pre-competitive collection of looking at something that we think would be very important. This is that study in pictorial form. Basically, on top you've got the surgery and on bottom you've got the sample collection and touch prep. You're sampling colon and liver meets at the same time that you're getting access to the tissue that you're looking at. You're also doing the blood assays; so, you actually can do these things together and simultaneously.

Out of this, we believe we'll get certain applications for stakeholders. I think we'll get high content bio-signatures which again could be similar to what we've seen earlier today characterization and interrogation of the liquid biopsy, and also for certain settings help with drug development.

Doesn't seem to want to advance. Oh, there.

Just one word on exosomes. We heard some today. We've looked at CTCs, CTDNA exit zones. As we started to look at this, it was pretty clear that there's not one clinical project or two where it's easy to do these all at one time. So, we're still thinking about the exosome. I think it's really important that it protects the RNA, and that is important because the RNA is where there's a lot of activity that you're not getting very easily from CTCs or CTDNA. Even though more and more single cell CTCs, you can get extracted functional RNA in the exosome to protect the RNA which otherwise is cleaved in the blood, except for the micro-RNA which we heard about.

The surface markers on the exosome are the same as the cancer cells they are budding

from. There suggests separation techniques that might be valuable. Certainly, we think it might be useful for both early diagnosis, and a number of laboratories are working on this, and there are, again, twenty or so folks that have exosome masses that are working out there.

One other point about exosomes, and we have heard a lot about blood today, but I think it would point out that there is work going on in urine, prostrate fluids, CFS. So, it's not just blood that we're interested in, and a lot of the context of uses might find their way in these other fluids.

This is Lou Stout, great scientist we have at NCI, and he likes to make the point that genomics is not just about primary sequence but among statisticians and mathematical modelers who have to deal with this huge block of data as well as the functional genomics related to what the DNA is making. This, we published a few years ago. I just want to say that we know and think that the biology is carried out at the protein level. If you look at what protein choices you have here, you only have 23,000 genes, but when you start looking at variance splice, variance, and post-[inaudible 00:17:48], the estimates are about a million proteins and cells. And a lot of them work on protein-protein interaction.

The biology is even more complicated than that. Really, at this point in development, you cannot fish out blood or serum or plasma proteins in a way, in its naked form, that gives you functional assays. You're really having to depend on going into tissues and doing the correlation of proteomics against tissues. When you do that, you're starting to find from TCJ that the proteins do provide information that's often additional and very valuable. Also, you heard earlier today that there is some protein assays that're being extracted from single cell RNA.

This we borrowed from Bob McCormack, our good friend Marty Flesicher who ... and I will just finish with a need for standardization. I know this morning, for three hours, I heard standards at least ten times. I think we all agree that standards are needed, and we are very interested at FNHI to create a standards protocol. Our leaders for this are Mickey Williams and Bob McCormack who know a lot about this. We've gotten this since the FDA and academia ... and we're looking really, very specifically to do a project that involves standards. The standards will be ... we would think this would be created by year end.

Certainly, there will be a white paper that describes what's happened. And also, we're very interested in a couple of examples of down stream clinical trials which would actually show the value. Finding that space is a function of where the opportunity is. The lung gets pretty well ... worked pretty hard and yet there's still a lot of things to do.

Next to last slide. CTDNA is going to find its way. It's predictive response, resistance, early detection, prognostic. We've heard it today, and I won't belabor. This is my last slide. We wrote this overview for drug information association. In 2005, we had a session on precision medicine contributed. There were six articles of different themes along precision medicine. In this last year for 2016, we wrote this again. I won't go over each word of this slide, but basically, on the challenge side you can see where CTDNA

and other liquid biopsies are going to play a big role in terms of a lot of the things that need to happen. With that, I'll let it go. Thanks, thanks.

Gideon: Okay, thanks Gary. Last we have Dr. Robert McDonough from Aetna. Tell us about where the rubber meets the road, how are we going to pay for all these exciting technologies.

Robert: Thank you. This presentation is just a brief overview of something they think that many of you, especially you involved in the early development, this might be the opportunity to go out and get some coffee or something. I know a lot of people's eyes glaze over on this sort of payer perspective, but really, if you want to think about the payer perspective as sort of the opposite end. I mean, so much of today's discussion is about the early clinical validation and the data that may be needed to get regulatory approval. Then, the payers come in either in the sense where there are situations where there is not regulatory approval in terms of laboratory developed test or in the situation afterwards where you're actually needing to get regulatory approval and then plan on marketing your product.

I am a member of the Aetna Clinical Policy Unit. Every benefit plan, for insurance, has language relating to things that are unproven or experimental. It's generally excluded from coverage with some exceptions. Any service that is provided has to meet plan definitions of medical necessity. Where did those definitions come from? They come from the plan documents. There are some generally accepted definitions that are pretty common. One of which was developed by the AMA and several other payers in an agreement with regard to how they are going to define medical necessity.

We actually publish what Aetna calls "clinical policy bulletins". Other payers call them "medical policies". They are published on the internet. They are publicly available. You may not be aware of them. Certainly, your billing office, if you're in practice, are aware. If you want to find them, you can just Google "Aetna medical policy", and whatever thing you're looking at, you're likely to get a hit if you can't find our website. The purpose is to be able to have consistent objective, supportable policy determinations. Especially with a larger company like Aetna, where we literally have thousands of nurses and hundreds of physicians making coverage determinations, there is a real need for consistency in being able to support our determinations.

Some of you that are more familiar with coverage policy, recognize this is the Blue Cross/Blue Shield Association tech criteria. These are sort of general criteria that payers use for evaluating all medical technologies. You'll note first that the regulatory approval is only one of the requirements. So, in many cases, there is not requirement for any kind of regulatory approval. If there is a requirement for regulatory approval, that would be part of the requirements. It wouldn't necessarily be sufficient for coverage. Then, also, there are situations, say with off label use of products, tests, drugs, etc., those would be eligible for coverage depending on the quality of the scientific evidence.

You have to have adequate scientific evidence. That also relates to clinical guidelines. We also consider clinical guidelines in policy development, but they are considered according to the quality of the scientific evidence in supporting rationale. Guidelines are

important, especially where there are gaps in evidence in order to be able to use expert interpretation, but they need to make scientific sense.

Health outcomes are really important to payers. As I mentioned, a lot of technologies fail at the point where they don't provide adequate data of clinical utility. A lot of times, the focus of all of this is on the analytic validity, the clinical validation, and the clinical utility data is often lacking. Technologies are compared to each other, and they must be as beneficial as other established alternatives. This final point, which is sometimes not enough attention is being paid, how is this technology, liquid biopsy or whatever, going to act, perform in the real world setting? That the improvement in the health outcomes must be obtainable outside the investigational studies.

That's something that we've been struggling with. There has been a lot of discussion. Just as we are having discussions here, there are payers having discussions about how are we going to evaluate these new technologies involving liquid biopsy or other new technologies in oncology. A lot of the discussion is about how are we going to use real world data to really find out how these technologies are actually going to perform in actual clinical practice.

This is just sort of a list for your reference of the types of considerations, point by point. Sort of a checklist of the considerations that a payer would consider in terms of liquid biopsy or other technologies. There's probably ... not particularly unimportant here is the benefit plan provision. For some technologies, that's an important issue.

There may not be a plan benefit for a particular technology but that certainly doesn't apply to diagnostic tests, and monitoring and staging tests for oncology which are a standard benefit. But what is important is looking at the experimental and investigational status of the technology. That gets into the types of considerations that you would consider if you were as a clinician making a decision about the types of data, about the analytical validity, the clinical validity, the clinical utility. Those are the same kinds of considerations that payers have to take into account.

Also, I mentioned the medical necessity part because once you actually have a technology, and you can prove it, there really is a question of defining the appropriate use. So, you may be able to have reliable data. Develop that; liquid biopsy might be able to be used in the recurrent setting, but there is going to be immediate interest in being able to use this for monitoring response to treatment. Or there may be interest in continuing to use this technology for surveillance purpose or for establishing a diagnosis. Defining the medical necessity is as important as determining whether a particular technology is proven at all.

Getting this third point about clinical policy implementation is probably as important. It's something that is not always well considered by people who are developing technologies. Something like coding has a significant impact on whether a technology's being reimbursed. What I mean by that is payers have ... most claims are adjudicated automatically. We have this language that we call CPT and HC-PC codes that define either the physician's services or the diagnostic tests, surgical procedures and drugs that a physician uses.

That's the way that physician offices and hospitals communicate with the payer. If a technology, such as a liquid biopsy, has one standard code that defines maybe several technologies from several different companies, it does present a dilemma in terms of do you as a payer ... are you aware that there might be some subset of providers of a technology that have a validated, well validated, well functioning test? And another set of companies that offer the "same test" that can be defined by the same code, but may not be as well developed.

It presents a challenge to payers because short of stopping claims and looking through our records, we may not even know what particular test, that's being defined by that code, that's being performed. So, the coding is really important. The coding also has to do with how we would adjudicate the claim. Are we going to, in certain limited circumstances, require actual precertification? By precertification, if you want to know whether someone is going to use, for example, a clinical test commonly used today is the Oncotype DX for breast cancer, and you want to know whether they are actually being performed in appropriate set of patients that are either node-negative or have certain limited node-positive disease in breast cancer.

That's something that cannot be defined simply by the coding. You actually have to, prior to the claim being submitted, require physicians to actually request and provide information about the test. Obviously, it's a very labor intensive kind of review, and hence, it's something that's fairly limited and in most circumstances, doesn't apply.

Finally, I think the things that are also important to reimbursement are things having to do with contracting. I think previously we had not, as payers, paid a lot of attention to the quality considerations. We would just assume that a serum test from a lab that's CLIA certified or whatever, would be a valid, appropriate test. But with some of these more complex tests that are being developed, there really is more of a need for payers to be aware of that. Not all tests that are being performed, not all liquid biopsies, even if they have the same code to define them are necessarily of equal quality.

That really creates a challenge for us to be able to determine which are the appropriate test providers that need to be in our network. The laboratory contracting also gets into the questions about reimbursement, the appropriate reimbursement for the amount of effort that's being provided.

Are payers going to just go with whatever provider, liquid biopsy provides whatever defined by the code at the cheapest rate? Or are we going to be able to look at situations where there are where quality should be taken into account. I certainly would hope it would be the latter, but that's where a lot of the work today is going to be able to help us. To be able to define the appropriate quality standards so that we can determine which is above adequate quality tests being able to be performed, to be able to accomplish the medical necessity, the medically necessary indications for that appropriate test. And also, developing the kind of data that would allow us to expand the use of the test beyond just the use in the recurrent setting to monitoring treatment response and all.

WE'll have time for further questions. This is obviously not everything that you need to know, but it gives you a brief overview of the basic points you'd want to consider when you're thinking about what happens after the product gets approved by the FDA and gets into the market, in terms of what the payers need to think about. Thank you.

Gideon: Okay, let's call up our panelists. While we're ... they're coming up, does anyone have any questions?

Girish: [inaudible 00:33:16] I drew the short straw. How about you?

Gideon: Yeah.

Girish: Or should I say ...

Gideon: Actually, let's start with Girish. Why don't you just state where you're from, and what you guys do.

Girish: I'm Girish Putcha, Director of Laboratory Science at Palmetto's MoIDX program.

Gideon: Okay. We have Dr. Beaver who you saw.

Julia: I'm Julia Beaver. I'm the Clinical Team Leader for the breast and gynecologic malignancies group in the office of hematology/oncology products at FDA.

Geoff: Geoff Oxnard, lung cancer, Dana-Farber.

Gideon: Okay great. Let's start with Girish. Can you explain a little bit about MoIDX and what you've been working on in terms of enhancing standards and quality and transparency?

Girish: Sure, first I wish we'd stop calling in "Moldy X" because that just doesn't sound good.

Gideon: It's like an exterminator?

Girish: Yes, exactly. As many folks in the audience probably know, we, about a year and a half ago or so now, had put forward analytical validation specifications for tissue based next generation sequencing testing. We've since followed that up in the beginning, earlier part of this year with specifications on liquid biopsy based, or liquid biopsy types of tests. I don't know, Gideon, if I should do it now, but maybe I'll take the opportunity to make a few observations?

As I was listening, there were maybe three or four points that sort of struck me as general themes. First, and these are going to be in somewhat random order, but first, this issue of education sort of both, physician and patient. What struck me here are some of the parallels, frankly, between non-invasive prenatal screenings and liquid biopsy based tests.

Specifically, what occurred to me is that a lot of the, some might say, irrational exuberance around an IPS in it's early days were, frankly, around the miscommunication

of the fact that those tests are intended for screening only. Just as an analogue on the liquid biopsy side, it occurred to me that this whole issue of what you do when you don't detect a variant is something, again, that I think the industry and practitioners and patients really need to take to heart in terms of understanding what the test is really intended to do and what its limitations are.

It also struck me as sort of interesting that we had all this conversation about CNV detection, and of course, those tests are all about CNV detection, but I would point out, obviously, that those are constitutional and not focal. So, point number two that others have brought up too, is that many of you are probably aware of this in terms of these reference materials. Many of you are probably aware in addition to the effort that the NCI was just talking about, there's also a group called Tapestry that is working with Amgen and Illumina as part of this thing called the SpotDX project.

That is basically trying to develop reference materials, or reference specimens is technically the terminology they're using, that will allow laboratories that are performing LDTs as effectively follow-ons for an FDA cleared or approved companion diagnostic to essentially assess the analytic performance on a common set of samples and then provide transparency. Again, the mechanism for that still needs to be determined but transparency around that performance.

Maybe in the interest in time, I will stop at the last one even though I have a few more ... come back to them later ... which is the issue of not letting perfect be the enemy of good enough. I really struggle with this. I think we all struggle with this in terms of balancing the evidentiary requirements whether that be for regulatory approval or payer reimbursement with the needs that Geoff and other's have sort of particularly discussed on patient care.

This is where we just have to acknowledge that there is ... We've created this vicious cycle where there is obviously this regulatory free-for-all with LDTs and IVDs. You've got ... that encourages or allows effectively anyone to claim anything, but then you've got a reimbursement system that doesn't actually value those who go out there and develop the evidence and provide good solid evidence. Which of course, in turn, leads to poor evidence development, the inability to distinguish a good test from a bad test, and we just keep going around and around.

I feel like, certainly, we keep saying this over and over again, but at some point we actually have to do something about this. I'll just throw out there as something that might be a little bit provocative, there seems to be a compromise here that is at least possible. There may be practical issues, but I'd like to propose, what if we effectively, to facilitate the innovation that we all say that LDT is and we understand provide in the industry, that an LDT is effectively allowed to be out there and marketed with the kind of transparency, third party verified transparency that we had discussed before.

Whether that comes in the form of a label or a LTD label or whatever, but that once an FDA approved test gets on the market for that same indication or intended use or whatever, somebody smarter than I can figure out what that ought to be. That those LDTs stop because otherwise we do not create a system that incentivizes appropriate

behavior. That incentivizes and provides a return on investment for those companies who will ante up and put forward the effort and the money and the time to do this well.

I will stop there. Thanks.

Gideon: Provocative. Thank you. So, let's change gears a little bit here. Julia, I just wanted to ... we haven't talked much about from the drug development side. We had a couple of drug developers earlier in the meeting. So, what are the mechanisms by which you can qualify a biomarker in a drug development program from an FDA perspective?

Julia: Sure. There are a number of regulatory pathways for acceptance of a biomarker such as CTDNA in drug development and in drugs. One, we've talked about being a companion diagnostic development where in this case, CTDNA would be deemed essential for safe and effective use of the drug. We also have a slightly newer criteria complimentary diagnostic which does not quite rise to the level of a companion diagnostic, but informs the risk benefit assessment for the patient. That could be included potentially in Section 14 of the drug label, the clinical trials section.

Then, as you mentioned, there's also the biomarker qualification program where a biomarker could become qualified in a drug development program in a given context of use. Then, could be used repeatedly in that context of use, would not need reconfirmation in the future. That's somewhat a more statistically rigorous process, and to date, there are no oncologic biomarkers that have been qualified yet. But it is a potential, and there are a number of the programs FDA has to help innovate biomarker development within the Center for Drugs through collaboration with CDRH one of which is the critical path innovation meeting. Stakeholders can request an informal meeting with FDA to discuss various biomarker development programs for CTDNA and garner together thought leaders in various organizations within FDA to have an informal discussion to try to spur innovation and drug development.

Gideon: Thanks. Let me turn over to Geoff. You're a PI on the Alchemist Trials, right? Is that, that's-

Geoff: I'm one of the study chairs, yes.

Gideon: That's a [inaudible 00:42:06] for EGFR mutant, non-small cell lung cancer in the [adogen 00:42:11] setting?

Geoff: Receptive lung cancer, geno-typed and then enrolled in the targeted therapy adogen trials.

Gideon: Okay. What's your take? You've also worked with Gary on public-private partnerships, the [inaudible 00:42:24] for example. What's your take on public-private partnerships? Are there any sort of mechanisms we should be doing now thinking from a government standpoint?

Geoff: How can we all get together on this and make headway? It is tricky right there. There's so few specimens. There's so many parties that want them and want to study them. It's

really competitive, patients and doctors feel in between all of these various places. It's an intuitive place where firm leadership from the NCI and FDA could help us get on track. How do we do that?

To some extent, sure Alchemist is an example of a trial where we are collecting a lot of tumor specimens. We're going to do lots of tumor genomics. We are adding to this trial plasma genomics to try to study minimal residual disease after lung cancer resection. It would be great a couple of years from now to have all this great blood to go out there and good science. For who? Who gets to do the science? Who qualifies? Who gets to graduate and gets to play with these awesome NCI invested specimens? What is the process through which the scientific rigor required so that someone could pass the test and say, "I've got the good test. Let me sign up.

Let me take a stab at this NCI invested trial to see if I have assay that can study the disease. I don't think we have any ... it would be great to be able to put those kind of hurdles together. Those kinds of tests to help compare for our scientific learning, for patient care learning, for paired interests the various assays out there and their various claims.

It requires good, contrived specimens, and I don't think there's good agreement on how one would make good, contrived standards. It would require really complex blinding of such samples and a third party who feels comfortable being the adjudicator in this bake off, who's not conflicted but going to actually test the different parties required. The parties being on board for proceeding with such tests, they all have confidence in their assays.

You'd think, if they're selling it, they could take the test. Intuitively, that would be great. The only challenge I have is that we kind of need it now, and we're just talking about it now. How can we do it in such a way that we could actually make it happen in the near term so that we all can start to feel some confidence in assays that actually in a third party test can substantiate their claims. Is that what you were asking?

Gideon: I'll take it.

Geoff: Okay.

Gideon: Okay, we can open up for questions. [Pikash 00:45:19]?

Pikash: Let me go to the money guy. How will you like to pay for the same test twice? I mean if ... in that, we heard in the CTDNA reflex testing, right? In the pathology lab, reflex testings means you get a biopsy, say gastritis, you do a reflex test following all the time. I want to see HNE and this ... that's what called reflex. So, ultimately, you will have some labs doing the same thing if it is the word reflex. So what's your thought about putting that reflex testing?

Robert: Well, it's not ... oh, thank you. It's not a concept that's alien to us. Is, you're right, the idea that reflex testing is something that's been used in laboratory medicine. So, it does present us the prospect that we're going to pay for a liquid biopsy in order to get an

early EGFR result, and then pay for a tumor biopsy's tissue sample later.

I think as long as it makes sense, clinical sense, it's something that payers will accept. If it seems to be completely duplicative and unnecessary, in some cases where it's not clear what the benefit is of measuring the same analyze twice in two different ways, then I think you're going to have challenges with the payer.

Male: [inaudible 00:46:50]

Robert: Right, and that's another thing. Goes back to the issue about coding is that we may not even realize in fact that we are paying for something twice.

Male: Twice is one thing. What if the patient getting that liquid biopsy every couple a months to look for resistance until it shows up over the course of months and months and months and years? Right, so, one of the problems I have with how this works is that when you get a tumor specimen and submit it for testing, you know that it is adequate.

We don't know about liquid biopsies [inaudible 00:47:26]. Is there any DNA? Is it an adequate specimen? You could be testing and testing and testing and testing and testing dozens of inadequate, scant, useless, non, no tumor specimens. Billing and billing and billing and billing. I think that's one of the challenges here.

If you know you were only testing adequate specimens as clinicians ... I am biased to send patients with low burden of disease that's hard to biopsy, has no shed and isn't going to be picked up. Those are the ones I'll always send first because those are the ones I don't want to stick a needle into because I can't which means, you're likely to get testing and be paying for unsuccessful tests. This is a conflict.

Robert: Right, and as you say the payer may not even be aware of that because think of the type of information that the payer would have to get to be able to determine whether what you're happening is occurring. So, it's going to be a big challenge, and I don't think I have the answer at how we're going to be able to address it.

Girish: To be fair, Geoff, maybe two comments. Look, we have to at least depend on each other to be honest. Labs eat the cost of that sort of testing all the time. Okay? They won't bill, but you have to make a choice to not bill if you get a sample that is inadequate. That's the idea of having as much up front QC as you can. I get your point about you might not know until literally the end of having run that test, but I can tell you as somebody who's directed these labs, you eat that all the time. And the question is how much? If 50% of your samples are inadequate, then maybe you need to be thinking about not doing that test or developing a different test.

That's one question, coming back to the issue about coding, Bob you know this well. I've said this over and over again. The CPT coding system is a complete and utter mess as it exists right now. The codes for these tests are completely inadequate to address the needs that we have. They cannot distinguish hot-spot versus completely genomic profiling. They cannot distinguish something that's basically just looking at something simple, easy from something that provides a lot more information on drug resistance

and therapies and everything else. But there are again, they're mechanisms, not to sound like a pessimist, but they are mechanisms by which to address this. And, that requires, again, stakeholder involvement to say, "This is what's wrong with these codes. These are how we can make them better."

Certainly, at least now with Pama there's the ability to distinguish for the first time in history - amazingly, this took us this long to figure ethics out - but to establish an FDA approve test in the codes from something that something that is not. So you can't reward innovation if you can't even identify it. That's the reality of where the payers are. Anyway, more to come.

Female: I'm coming from a drug developer perspective. The question I have is maybe a little bit naïve from a regulator's point of view, but referring to the case that was presented for the [Kobis 00:50:13] test, the first now approved liquid biopsy test for EGFR mutations, we know that their validity and the clinical utility has been demonstrated in a lot of new data. However, there are other drugs for which tradition of it, mutations would be predictive for their success.

My question is, would the developers of those drugs, can they automatically claim that now that the FDA test is available, there is something to detect these patients, we can benefit from it as well and the patients can benefit regardless of whatever drug they go and to use in this space? Do they actually have to demonstrate clinical utility with their data as well before they claim it?

Julia: [inaudible 00:50:55] on the lung cancer?

Geoff: Sure. I think in general, it would be hard to ... If you have several drugs in the same class and one goes through the clinical validity, analytic validity, submits the package to FDA and gets the labeling claim, it would be hard to just have all the drugs in that class automatically get grant further into that claim. There would be some expectation for a package. Not to say you cannot potentially leverage data from other development programs but there would have to be independent programs.

Julia: I believe for some of it too, companion diagnostics, that was the case.

Male: I want to ask ... I heard about [Bakeoff 00:51:52] and third party vendor with grading or emojis to talk about the quality of the testing. Does anyone in the panel have any thoughts? Who would this third party vendor be? Any thoughts?

Girish: Let's be honest. The choices are pretty limited. The most obvious ones are probably the College of American Pathologists. At least to me, that would seem to be the most obvious. In terms of other entities that could do this, even might do this, New York State Department of Health is obviously. Another possibility, as I see, you're shaking head. Of course, the FDA.

Look. The reality is there are very few bodies that has a mechanism, obviously through their proficiency testing program to be able to distribute in a blinded way to laboratories materials. Part of it is you have to get the right materials. Part of it is it's not

required that you'd be accredited to perform this testing. Certification is enough. Yeah, obviously, there has to be some regulatory reform and there has to be some infrastructure built up but the mechanism exist.

I guess, the last part of it is of course the transparency. The labs that perform [CAP 00:53:20] proficiency testing, you go try to find out how they actually perform. Good luck with that. That's the reality of the way it is. If you are a lab, you cannot get the information but it's aggregated. You cannot say, this test is good and that test is good or this lab is good and that lab is good. All you get is they're CAP accredited or they're not. That's it.

Male: Gideon, can differentiate claims or is it just CAP total?

Girish: It's CAP total. The reality is CAP doesn't ... They have it. They have the ability too in terms of their checklist to evaluate the test, but technically, they really do more about evaluating the lab as opposed to the test. New York obviously splits the two and does both, but then again, how does the test perform that's got in New York state's approval? If you find out, let me know.

Male: I was a bit [thrown 00:54:11] by the answer you gave to the lady. Here, we have defined molecular change which all the drug had been developed and you would say, they would have to go and do a clinical study. Why could they not do an accordance study with the [Roach essay 00:54:28]?

Geoff: Again, there is a mechanism potentially for follow on companion diagnostics. I don't know if Reena has any comments on that but I think, again, not to sound coy but a lot of, it would be a review issue. Come talk to us.

Male: Okay. That's fair enough.

Female: I actually do have a question picking up on a couple of comments that people have made which is essentially running a situation where we have a regulatory framework that works on the premise that you have one drug intertwined with one test using one technology if you want to extend that analogy. But the real world, what we're facing is technological innovation that's moving ahead rapidly which is spurring from the investigator's perspective, the patient perspective, the physician perspective, the need to maybe decouple this and get to a situation where you can have test and drug development moving along in parallel with technology such that you seamlessly integrate all three of those.

I know that right now, we don't have the regulatory framework that adequately captures that. Then, it becomes a chicken and egg situation, right? How do you seamlessly rethought together? I'm not even bringing in the pair thing. I'm not going there. I just wanted a sense from the stakeholders just to have it ... I mean, we do have to get together and talk about this because otherwise, we're going to have this exact same conversation. Today, it's about liquid biopsies. Tomorrow, it will be about something else. This is exactly the conversation we will have three years from now. I just wanted some feedback on this from all of you.

Gideon: Any takers?

Female: It's actually a follow on question to Gideon which is, isn't that the whole concept behind the Cancer Center of Excellence, which was to bring the different agencies together to smooth out the regulatory process?

Gideon: Yeah. You would know as much as I do but now, I think you're right. This is still in its embryonic phase so who knows how this is all going to shake out but yes, absolutely, definitely to facilitate Dr. [Pazdur 00:57:10], acting director of the OCE. One of his charges from the [moonshot 00:57:17] is to streamline communication across the centers.

Girish: At the end of the day, it's balancing risk and reward. We got to figure out to some extent as a community and this is where obviously the patient advocates and I think the providers on the frontline of this can say, "Look. This is the real world. This is what we need." I just think, we want to again build the system that encourages the kind of evidence and rewards, the kind of evidence development that we're asking.

We seem to be okay waiting for drugs to pass these hurdles or other medical devices to pass these hurdles. We're not comfortable with doing that for diagnostic test but I feel like if you do that risk for calculation, maybe we have to reset and this idea of having tiered levels of claims. Their clinical claims associated with certain things and analytical claims associated with other things, there's a path there.

I think everybody can see it. The question is whether the regulatory agencies are comfortable doing it, whether the payers are comfortable, then again, incentivizing that behavior by recognizing it and rewarding it. This is the kind of conversation where that happens.

Male: If I could just comment. We've had lots of discussions at MoIDX which [inaudible 00:58:36] but clearly laboratory industry has just not taken upon themselves to prove this perspective and show clinical utility. This very clinical utility you show now.

That's not technically their fault because clearly, laboratories tend to be paid and they have you the reimbursement should be equivalent to the cost. If the pill company produces cost a few hundred bucks and I get \$10,000. The system is broken.

What we have to do is try and bring all the phase together, the FDA, the Moonshot, and develop a perspective clinical utility ability somewhat subsidized with coverage, with evidence development even data collection somewhat subsidized, in my opinion, by the Moonshot because precision medicine will never get anywhere unless we're able to enable even a young guy in a lab versus a big company test something.

If a committee agrees on clinical utility, it's got potential to clinical utility be tested respectfully. They haven't got the resources. Some companies do but the majority do not. Most of all, at the end of that, put a value to the test so they get rewarded.

Gideon: Right. Actually, that's a great point. I like to ask, what would be, for a coverage with evidence development, what would be evidence of clinical utility? What would you need to demonstrate to show utility?

Geoff: There's two parts of the question. One is coverage with evidence development and the other is clinical utility. Girish probably comment more about coverage and evidence development because Medicare is much further than commercial payers in terms of providing coverage with evidence development.

The question is, can we infer clinical utility based on data that's indirect. The most obvious of providing data and clinic utility is to do a study that looks a lot like a drug trial, but I think we're struggling with the fact that they maybe impractical. There maybe situations where we can use information indirectly where we find good correlations between, say, one type of test and another test is being replaced where there is good established clinical utility for the other test.

In the case of liquid biopsy, there maybe situations where it maybe just the analytic and clinical validity is sufficient because the clinical utility of the marker is well known. But there are going to be situations where I think there is going to have to data more along the lines of the type of data that you would have to have to develop any other technology and new medical device or a new therapeutic intervention in terms of the type of perspective clinical data that we would desire.

Male: I think clearly this low hanging fruit, diagnostics, but as you've mentioned, if you want to have a therapeutic improvement and outcome with a drug action, that's an expensive trial. It has to be subsidized some way if we really want precision medicine and liquid biopsies to reach their full potential because the answers and the potentials are very complex. Gideon, as he said, the MolDX program is really, we decide on what the space is, what the potential clinical utility could be.

There were some liquid biopsy proposals coming before which we're reviewing. If we think they're analytical performances evaluated is adequate and their clinical utility proposal have value, we will pay for the test and continue to pay for it if it reaches its end point at the end of time period analysis. That whole thing needs to be expanded. We need all of Medicare to really support it. The problem with the private pay is that they got contracts with companies so that it would theoretically increase premium of it and all of these complexities.

Girish: Really quickly, I don't know ... Jim [Omost 01:03:30], are you out there still? Maybe not. I was going to say, I should probably stay in my usual disclaimer but I'm not speaking for Palmetto MolDX or CMS. The reality is, CED, coverage with evidence development, is under statue only permitted by CMS. There are very specific requirements at that level for them to do it. Again, it's basically a clinical study. It has to find statistically driven end points.

I think we would probably all agree or maybe many would agree that that makes sense because the whole idea ... I mean, CED is almost like post marketing requirements on the FDA side from my naïve perspective. It's just to say, we believe that there is solid

analytical validity, reasonable clinical validity. In this case, called clinical validity and clinical utility maybe the same. It's just preliminary evidence of clinical utility but to do the study that we really think needs to be done, that's where we go at risk, you go at risk. That's, again, to me is it would to use your problems but it's a regulatory issue that we will take under consideration or something to that effect whatever your language was.

Gideon: Well said.

Girish: I review issues.

Gideon: Okay. Thank you to the speakers and panelists for Panel IV. Maybe, Pasi and Reena, if you want to come up. We have a couple of minutes for ... [crosstalk 01:05:06]

Reena: Thank you for staying until 5:00. I think it was a great meeting. Do you agree?

Male: Yes.

Reena: I just want to say that, this was planned almost a year ago and it was put off for several reasons. I really thank Nicole and Ana and Pam Bradley from FDA. They put together a lot of effort to have this great meeting. Really, kudos to them. All the panelists, I think, and speakers, we had several conference calls to put together this great meeting. Good job to all the panelists and the speakers.

Gideon: I just want to echo with Reena said, thank you all for staying. I think this is a really informative meeting and brought to light a lot of the issues that all of us are dealing in this field from a clinician side, drug development side, regulatory side, device development side. I think, more discussions to come for sure.

Male: Thank you.

Gideon: Thank you, everyone. Safe travels.