

**Presentation of the Comprehensive Map**  
*Clifford Goodman, Ph.D.*

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DR. FERREIRA-GONZALEZ: Before we begin our discussions of the recommendations, Cliff Goodman and his team of analysts from the Lewin Group will present a comprehensive map of oversight of genetic testing that they have prepared for us.

As you will recall, the development of a map is part of the Secretary's charge. So we want to review it with some detail this morning for two reasons. I think it will frame our discussions if we have a very good understanding of this map of oversight, and it will be a good primer for the work of reviewing the recommendations.

We want the Committee to weigh in on whether the map fulfills the charge of the Secretary. So remember to keep that in mind.

Cliff actually will be joining us from Rome. We seem to be working with the people that get to travel to very fun places and we are all here in Washington, D.C. Maybe we should ask Cliff to bring us something back.

DR. GOODMAN: I will do my best.

DR. FERREIRA-GONZALEZ: Staff is here. They have worked tirelessly to help us develop this map for the presentation.

Cliff, welcome. Please continue with the review of the map.

DR. GOODMAN: Thank you very much, Andrea. Can you just tell me now if this is a proper tone for my voice? Is it clear enough?

DR. TUCKSON: You are very clear.

DR. GOODMAN: I will proceed, then. You should have a title slide in front of you, Slide No. 1, which says "Comprehensive Map of Genetic Testing Oversight." We will proceed to Slide No. 2.

As you can imagine, this map can be quite complicated. What I would like to do now is present it at a very high level. You see in front of you five main sectors. As a matter of fact, if you want to extend the analogy of a map, you can think of five main continents of genetic testing oversight.

The five main continents start out with research and development on your left. Then, in the middle are three. CLIA-exempt states, which would be New York and Washington in particular. In the center is the main CLIA pathway, and at the bottom is the FDA pathway. At the far right is the sector for availability and reimbursement. Those are the five main sectors of the map.

Am I still being heard clear enough at this point?

DR. TUCKSON: You are very clear. You are completely locked into the slides. It is as if you were in the room.

DR. GOODMAN: Thank you. Thank you, Dr. Tuckson. Let's go to Slide No. 3.

You will see now on the far left the research and development sector is highlighted. What I'm going to do now, with the help of our team, is describe each of these individual sectors of the map, these five sectors, and then we will pull them all together in the final slide. So let's proceed to Slide No. 4 now.

This is the research and development sector. We will talk about this part of the map and I will walk you through the main parts of it. We don't have time to walk through the entire bit of it.

We will start in the upper left with "Understanding Gene-Disease Interactions," with "Basic Research," and then a cycle of prototype design and preclinical development. Coming out of pre-clinical development, we are going to do clinical testing, perhaps, of devices.

You can see towards the top where it says "Test Clinical Development." You can arrive there directly from "Pre-Clinical Development," although in some cases you may have to arrive from just below where it says "Apply for IDE." That is investigational device exemption, which may apply to certain tests and test kits and so forth. That is the permission that is needed to test a device, including some tests, not all, in people.

So that is how you arrive at the clinical development of tests. Extending to the right from where it says "Test Clinical Development," you can go directly up to LDTs, which are laboratory-developed tests. That is one route. Now, going down from there, you will see down to "IVD/IVDMIAAs." This group of course knows what those are. That route is typically, but not always, typically characteristic of test kits and test systems developed by device-makers and other companies that will manufacture these. So those are two routes for devices.

Now, you will notice, quite interestingly, where it says LDTs there is a downward-pointing arrow. That downward-pointing arrow toward IVDs and IVDMIAAs reminds us that some LDTs are IVDs or IVDMIAAs, and these, as you will see later, are going to be subject to FDA review as well as CLIA oversight. So it starts getting a bit complicated there, but it is important to understand, especially in light of the more recent FDA guidance on IVDMIAAs. Indeed some laboratory-developed tests must be subject to oversight that way.

Now, going back toward the top where it says "LDTs," you will see that this breaks off into three main directions. One is going to be the CLIA-exempt state route. The next one is the "Available for Use" route directly. By the way, the secret that you will find out later on is [this is] the direct route for direct-to-consumer tests, which end up bypassing a lot of this oversight. That is a gap that the Committee has noted. Then the straight CLIA regulation is that third arrow off to the right.

Now, before we leave this slide, I want to remind you of a couple other things. If you go back to where it says IVD/IVDMIAAs, there is an arrow dropping down from class designation. For example, when a test kit company applies for FDA review, they will put it in as a Class 1 device, Class 2 or Class 3 device, and that goes in towards, at your lower right-hand side, application for FDA approval or clearance. FDA approval is typically for the PMA route, the pre-market approval route. Clearance is typically for the 510K route.

Before we leave this slide, notice that at the bottom we have provided a pathway for co-developed therapeutics. Co-developed therapeutics may be new drugs or perhaps biologics that may be developed in parallel to certain tests, certain genetic tests in particular. Although we are not going to dwell on the therapeutics very much at all here, we wanted to note here that there is a

place in the map for that co-development. Indeed, coming out of Phase 1, 2, or 3 trials, they too will go in for application for FDA approval as appropriate.

Before we leave this slide, I just want to remind you that you will see a double asterisk at the bottom left-hand corner of this first slide which says "Functions of FDA Quality System Regulation." You will see on this slide FDA design controls are accounted for as basic research and prototype/design. Later on you will see two other functions of FDA quality system regulation, or QSR, subsequently.

That is what we are calling the research and development sector of the map. Note towards the top something that says G2, where it says LDTs. G stands for "gaps," and in an accompanying document that I think you have perhaps in hard copy, we have a list of more than 30 gaps in genetic testing oversight, which gaps were identified by the taskforce.

For example, a very important one is the one that says "GD2." That refers to insufficient clarity about FDA role in regulating laboratory-developed tests. Of course, the report goes into that in much greater detail, but this map shows, obviously, in very short form more than 30 gaps and that is one of the more important ones that appears on this sector.

If it is okay, Dr. Tuckson, I will move on to the next sector.

DR. TUCKSON: Please do.

DR. GOODMAN: On Slide No. 5, you will see that we have highlighted "CLIA-Exempt States" at the top center.

Let's then turn to Slide No. 6. This is the CLIA-Exempt State sector. This applies primarily to New York and Washington States. We are going to start at the left, not the lower left-hand corner but the left middle that says "CLIA-Exempt State Regulation," for example New York. We will start there. We are talking here about CLIA oversight of the laboratories themselves.

That right arrow goes into a sector that has five main sections, starting with Proficiency Testing, down to Quality Assurance, Quality Control, Personnel Standards, Reagent and Equipment Inspection. This aspect of the CLIA-exempt state regulation applies to those attributes of these laboratories.

You will note that coming out of there, towards the bottom, just below "Personnel Standards," is a right-going arrow that points to "Analytical and Clinical Validity Review." Of course, if you look at this field, you know that there are some special things about the CLIA-exempt states with regard to their examination of analytical and clinical validity review.

Then you can go upwards, where there is the function of New York lab approval of non-FDA-approved tests, which is a very important function.

Upward from that is the New York State Licensed/CLIA-exempt, and then coming out from the right of that, to the right and down, is the route for availability for clinical use.

Now, in order for these tests to be available for clinical use, they do have to pass through this New York State licensed/CLIA-exempt. That is the pathway there. As a matter of fact, if you look at the lower left-hand part of the slide that says LDTs, remember this is one of the pathways from a previous sector slide. Those LDTs progress to the right and up, and those are the ones

subject to analytical and clinical validity review that do go through the New York lab approvals, non-FDA approved tests, and therefore can be provided by these New York State licensed/CLIA exempt laboratories. That is the route.

What has to happen for the test to be available for clinical use is that it has to have come from the LDTs and then be subject to the oversight of these laboratories. Once the laboratories subject it to that, it can then provide these tests. That is what we are trying to show.

The last thing to point out in this slide, which is in the right-hand corner, is of course biennial inspection. That is another aspect of oversight in these states. If a laboratory does not do well for the biennial inspection, there are certain sanctions. They may lose their CLIA-exempt status in some cases, or they might not be able to offer certain tests. You will see that the feedback loop goes back towards the CLIA-exempt state regulation function, and as a matter of fact, you can go all the way back to the "LDTs from Research and Development" in the lower left-hand corner because maybe data and information from that inspection can be fed back even to improve test development.

So that is the look at this one. I will just mention a couple of gaps. You will see in the center, just above "Proficiency Testing," those are Gaps 9 through 11. These have to do with insufficient resources, funding, and need to develop proficiency testing for all genetic tests. Gap 10 is that no data exist on the effectiveness of PT versus alternative assessment, and No. 11 refers to PT based on test methodologies such as sequencing that has not been fully developed in the United States. So these are some excerpted gaps from the text of the report.

That is the CLIA-Exempt States Sector. Let's move to Slide No. 7.

DR. TUCKSON: By the way, you are doing just great. There is something you just said at the end I want to make sure everybody understands. The gaps that you have so specifically identified and mapped to the map all come from the body of the report.

DR. GOODMAN: Yes.

DR. TUCKSON: You are summarizing the report. I think it is important that people understand whose words you are using. Thank you.

DR. GOODMAN: Yes. Dr. Tuckson, just to be even more clear, we did some paraphrasing and shortening, so we tried to find the kernel of the discussion of the gap to list it in short form on the accompanying single sheet. They do indeed come from the report, yes.

Let's move, then, to Slide No. 7, which is the CLIA sector, and then Slide No. 8, which describes it in more detail.

On Slide No. 8, let's start again toward the near left, which is "CLIA Regulation." You will see that that points to about five functions there. Some of these should be familiar already: personnel standards, quality assurance, quality control, analytical validity, and proficiency testing.

Now, coming off to the right here where it says "Quality Control," you will see "Inspection Survey Requirements." These can be done by CMS or its agents. Then, to the right, "CLIA Accreditation." So an important thing to consider again is the CLIA regulatory oversight of the several functions, along with inspection survey requirements, gets a laboratory to CLIA

accreditation. That is not the same thing as approving the test, but a laboratory with CLIA accreditation will be a laboratory that can provide the test.

As a matter of fact, the tests come in from the upper left, where you see "LDTs from Research and Development." Remember this was one of the other pathways from that sector. It comes across the top of this sector and down to "CLIA Accreditation." So what we are trying to portray there is the tests, as services, become available from the CLIA-accredited laboratories which have gone through those other bits of oversight, the several that I just mentioned. Then, off to the right, they become available for clinical use.

Once again, coming off the bottom of "CLIA Accreditation," you will see "Biennial Inspection," "Review of Validation Data" for all the tests, and again, an analogy towards the previous slide. If biennial inspection does not go well, the laboratory could lose its CLIA accreditation or it may not be able to offer some tests. That gives very important feedback information to the CLIA regulatory process and yet even again to the R & D process in a sense in that you learn from biennial inspection and other sources of data that may inform test development and improvement in the future.

Before leaving this one, I want to point out some of the gaps. We don't have time for all of them. You will see just above "CLIA Regulation" at the left Gaps 3 through 8. Of course those correspond to Nos. 3 through 8 on the list. Just to name one, Gap 6. I think there is a lot of emphasis on that one, which is insufficient resources to establish analytical validity, clinical validity, and clinical utility to address gaps in evidence for an increasing number of genetic tests. That is one of the important gaps to call attention to there.

For example, towards the far right-hand side where it says "CLIA Accreditation," Gap 12, insufficient regulation of laboratory-developed tests prior to initial clinical use along the CLIA pathway. That is another one that rises from the report.

That is a pretty quick run-through of the CLIA part of the map. Let's go on, if we can, to Slide No. 9. This is where we are going to highlight the FDA sector of the map. This is how it ties in.

Then, on to Slide No. 10. Let's start at the upper left-hand corner. Now, you will recall that we got to this part of the FDA sector from a couple of directions. One comes in from the top. There is a downward arrow to IVDs and IVDMIAs from research and development. Those can come typically from device-makers with test kits and test systems, but remember that some of those might be, for example, IVDMIAs that are laboratory-developed tests. That is, LDT IVDMIAs. Remember that they too are subject to FDA oversight in this model.

Also remember toward the left that it says "Co-Developed Therapeutics." Remember that we also have that parallel pathway for drugs or biologics that may be developed along or in parallel with the tests. So both of those converge on applications of FDA approval and clearance.

Now let's take the device part of this first. To the right of "Application for FDA Approval and Clearance" you will see "PMA" at the top. That is the pre-market approval application. Those are novel devices for which there is not a substantially equivalent device on the market. That is usually the steepest route to take for tests.

You will also see at the bottom of that box the 510(k). Those are the substantially equivalent tests. That means that something has been on the market or that something had a predicate as of 1976.

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There is also this special route to 513(f)(2), which is a way to get something called the de novo 510(k)s. That is when a device does not have a predicate on the market but it does not present a high level of risk. It is perhaps a way to not have to go through the full PMA route but using something that looks more like a 510(k). It is called a de novo 510(k).

In any case, these are all subject to, above, FDA manufacturing controls, FDA pre-approval inspections, and so forth.

Coming out of the right-hand side of that, you see to the right and down towards "Application Review," that is when it is reviewed by the FDA. Then, well, what is reviewed? Depending on the technology, it may be analytical validity, it may be safety and effectiveness. Of course, that is a very simplified way of saying the kinds of things that the FDA is looking for. When appropriate, the technology can gain FDA approval, which is typically for PMAs; clearance, typically for the 510(k)s; and onward to availability for clinical use.

You will notice, by the way, just below and to the left of "Available for Clinical Use" is the "FDA Post-Approval Inspections." That is another aspect of the FDA QSR.

Not to forget at the bottom, of course, was that route for the co-developed biologic. The BLA is the biological license application. The NDA is the new drug application. That is what you need to submit to the FDA in order to get review of these products in order to go to market.

So again, I hope you see that this is highly simplified to show these parallel paths going through one gate first, the approval and clearance. There is really a lot more going on there.

I believe those are the main points here insofar as the FDA routes. A couple of the gaps, to the far right just below where it says "FDA Approval/Clearance." You will see G6 and G14. We have already mentioned G6 before, about the insufficient resources to establish analytical validity, clinical validity, and clinical utility. Gap 14 is insufficient evidence of clinical utility for most tests. So remember, even when we go through this process, it is really the exception when you get good data and good evidence on clinical utility. So that is a very important gap to point out here, and I know that this is reflected in other discussions.

If we may, then, let's look at Slide No. 11. That is, as you see, the 30,000-foot level. We are going to take a look at availability and reimbursement. That is the far right and fifth and final sector here.

On Slide 12, let's start at the top. You will recall that we entered this sector from four different main pathways. One was from the CLIA-exempt states, New York and Washington. There is a route to get here by that way. Another one was that special bypass one, direct-to-consumer tests. That one is by non-CLIA-certified labs, typically. That is a pretty good bypass of the system and of course your report has called attention to that. The third one is from CLIA regulation. We have discussed that. The fourth main one is via the FDA approval, or current way.

There are four main ways to get into this sector, and just advancing up toward the top where it says "Available for Clinical Use," that is how they become available for clinical use.

Let's drop down from there. You will see that you have DTC, which is direct-to-consumer tests, and DAT, which are direct-access tests. Remember those difference between those. The DTC tests can be acquired by consumers, tested by themselves. Direct-access testing is typically something done by consumers but it should go back to a laboratory.

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Then there is clinician testing and testing by a laboratory, and so forth. Those are the several main ways that something becomes available for clinical use. You will see to the right of the DTC, DAT, Clinician, and Lab that those various agencies and organizations had various types and levels of oversight and other involvement in how these things are done. Obviously, the FDA. The FTC has a role of course. The courts do. Certainly many professional organizations. We noted other laws and guidelines. With HIPAA. We put a question mark after GINA because obviously that is still pending.

Now, having gone through these kind of gateways to become available for clinical use, you can drop down. Some tests to the right are subject to clinical utility review. This is really a very highly select number of tests. The U.S. Preventive Services Taskforce looks at some of those. EGAPP has looked at some of those. These are good but pretty limited efforts. Most kind of go the left way, which is not really being subject to another look at clinical utility that carefully.

Coming off the bottom of that towards "Reimbursement" and the right, there is an arrow going to "Reimbursement." Obviously that is carried out by Medicare, Medicaid, private insurance, the VA, Department of Defense, and others. That goes into "Reimbursement."

We don't show a bunch of other arrows from "Reimbursement" to all the places where the money goes. We thought that would be too complicated. I think you know where those go.

Interestingly enough also, another arrow goes to "Post-Market Surveillance" off to the left. This is done largely but not entirely by FDA.

So what you have here, then, is some post-marketing surveillance. There is a lot of feedback information from that. Some post-marketing surveillance information is fed back to reimbursement because payers are interested in what happens to tests once they are on the market. It might affect their coverage and payment decisions.

Certainly, post-marketing surveillance feeds back to the left, to the research and development sector and even the FDA approval part because post-marketing surveillance information may be used to reapply for perhaps a broader indication at FDA or may change how the FDA couches its indications or labeling for marketing of tests and availability of tests.

Notice, too, that at the very top it says "Outcomes Research." I don't want to forget that. Once a test becomes available for clinical use, various organizations in the public and private sectors conduct outcomes research. The findings of outcomes research may be fed back right to availability for clinical use. Clinicians and others may use that information to reinform their decisions about when and how to use a test.

Off to the right from "Outcomes Research," there is feedback that goes all the way to reimbursement. Remember the payers are also interested in outcomes research. It may affect their decisions. Outcomes research can go all the way back, along with post-marketing surveillance, to the R & D sector and input to FDA decisions.

So that is the overall picture of the FDA part of the map. I want to call your attention to just some, not all, of the gaps. Let's start at the top where it says G15 and G16, next to "Availability for Clinical Use." G16 is that there is a growing number of genetic tests that are offered based on inadequately validated genetic association studies. That was one thing that came out of the report.

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Let's go down to the lower right-hand side where it says G32 and 33. G32 refers to inadequate, outdated systems for coding, coverage, and payment for genetic tests and services. G33 raises the potential for misuse of genetic information in insurance premium-setting and employment decisions. That is a concern of some, and that is why I know that some people are interested in GINA, for example. So we are calling attention to a selection of the gaps that are noted in the report.

That is the FDA sector really quickly. Now, if you are brave enough to turn to Slide No. 13, Slide No. 13 is the big picture, where we put all of these five sectors together. I hope you realize why we didn't show you this first. It would have given me an upset stomach, I know, myself.

This is all of it put together. I want to say a few things about this before turning it back to Dr. Tuckson. This map does try to represent the current system. Is it complicated? Yes. Is it a simplified version of reality? Also yes. This is not a map to represent where we need to be or some would like to be or some ideal. It is a decent, high level snapshot of where we are now.

Why is it complicated? Well, it is complicated because it has to accommodate a great, evolving diversity of testing and testing services that have evolved over time. It also has to reflect an uneven and sometimes patchwork history of legislation and regulation that have applied to testing over many, many years.

So it is not complicated by design. It is complicated because it has to account for an extraordinarily diverse range of technology and it has to be complicated in order to reflect the different historical reasons and growth by aggregation of types of oversight.

That is where we are with this map. This map still needs some tweaking and some fixing. Obviously, we welcome more input for it. We will make it better, but this is where we are now. Back to you, Dr. Tuckson.

DR. TUCKSON: Thank you. I will give it back to Andrea in a second here. First of all, my God.

[Laughter.]

DR. TUCKSON: First of all, what a terrific job. I think the companion code for the 33 gaps is actually terrific as well. You sort of have those side-by-side.

Two comments I think that the report is going to need as we go back and look at it. Number one, at one level this in and of itself could be proclaiming a problem. Just the very nature of something as awesomely complex as this could by itself be declared a problem. So one of the things we will need to do also is to say how different is this than the oversight of non-genetic tests, which would be kind of important. If you were to look at this in the reality of traditional medicine today, is it any less horrible than this looks.

Secondly, I think that one of the things we have to be real clear about, and again, obviously we are getting into the basis of our analysis, is who is the person responsible for making sure for the public that all of that stuff gets dealt with. Once you start to realize that it is this complex, who is driving the train? Whoever is responsible for driving the train is going to have to be also fairly explicitly known so that folks will understand where are the accountabilities for the things that exist as we deal with the accountabilities for the things that don't exist.

Andrea, take it away.

DR. FERREIRA-GONZALEZ: Thank you. This map is describing a very complex process. I think it looks very complex because we have been very comprehensive in looking at the oversight of all laboratory-developed tests and the IVD and MIA route of the clinical laboratory testing that is currently offered in this country.

I would like to open the floor to see if anybody has any comments to the oversight map.

DR. TUCKSON: By the way, one other comment I had, as people start to rush to the microphones, is I think one of the things, also, that I wonder about -- and Andrea, I'm not sure whether we have commissioned Lewin to do this -- is a couple of illustrative vignettes. I think that [is] one of the things we probably ought to be doing as we have our debate and discussion about these recommendations.

For those of you that feel strongly about certain positions, play out a scenario so that you can actually see how this works in real life. But I think the vignettes are going to be very important for transmitting this report.

DR. FERREIRA-GONZALEZ: I think that is a very good idea. Does anybody else have a comment? Paul.

DR. BILLINGS: Reed mentioned the issue of genetic exceptionalism, really, in relation to the complexity of this. We have two other overarching issues: public awareness and access. I would say also fostering innovation. So I think that, actually, there ought to be specific comment about how this picture relates to those issues when this is portrayed.

DR. FERREIRA-GONZALEZ: Muin.

DR. KHOURY: This is a very nice and complicated view of the real world. We can all quibble about little things, but just the fact that we have all the map laid out is a very tremendous task. My compliment to the Lewin Group for doing this.

I just want to, by way of clarification, try to understand how the LDTs, like Decode Me and 23 and Me, just go straight to the consumers, bypassing all of this. I don't quite understand how this happens right now. Maybe because they don't use it for health purposes? Basically, there is a big hole. There is a train you can drive from an LDT directly to the consumer through all of this complicated framework. Maybe somebody can explain it to me.

DR. FERREIRA-GONZALEZ: I think that you have just identified another issue that the Committee had and that is exactly portrayed in that way about the LDT for those laboratories that are offering testing to the public without going to CLIA certification. They claim that they don't fall under CLIA statutory regulation here. So that is exactly what we have here and that is a big hole that we have identified.

DR. EVANS: Isn't that because they claim not to be offering diagnostic or medical services?

DR. FERREIRA-GONZALEZ: Remember we have recommendations on that issue. We are just looking at how we are portraying that type of test. Steve, do you have a comment?

DR. GUTMAN: Yes, I also applaud this. It is amazing. However, it is not complicated enough.

[Laughter.]

DR. FERREIRA-GONZALEZ: Do you want to complicate it?

DR. GUTMAN: It leaves out what to us is a small but important niche line of submissions, which is the investigational device exemption, or IDE exemption. That clearly needs to be interposed. There are some technical corrections. I won't bother the Committee with that.

DR. FERREIRA-GONZALEZ: If you can give us the technical corrections, it will be greatly appreciated.

DR. GUTMAN: I will provide them. In regard to post-approval products, our surveillance program, post-approval, or pre-approval, PMAs, or pre-approved, the de novo goes straight. You don't break off to PMA. Actually, that is the whole purpose of the de novos.

We would probably take umbrage. I realize that this is hotly contested, but we would probably call LDTs IVDs as well, but they are IVDs to which we have applied enforcement discretion. So we have a variety of small things.

DR. FERREIRA-GONZALEZ: The idea is to identify the different roles.

DR. GUTMAN: The missing IDE is, for us, is a patient protection vehicle that you need to think about when you do look at the whole map.

DR. FERREIRA-GONZALEZ: Phyllis.

DR. FROSST: I would of course like to echo the comments that have gone before me at how impressive it is to put together a map of this scope of detailing, a process that is clearly very complicated and likely to become more complicated as the map evolves.

My first question determines what my second question is going to be. The audience for this is the audience for the report, a fairly high level with, hopefully, other people in the field reading it to understand it. So the report is twofold, an in-depth analysis of the situation with recommendations for that so that a more casual reader could understand it.

My second comment would be that I think one of the most valuable parts of this in looking at everything from a 30,000-foot view is having gaps tie in with the process. As a casual user, I would see this diagram and I would flip the page. I realize this is a very non-trivial thing to be thinking about, but would it be possible to do a map of this flavor at a lower resolution, at a higher view? Very much in the way that you broke down each chunk into chunks, can you collapse some of this granularity into a way that someone could appreciate where the gaps are without losing the understanding of what the process is?

DR. GOODMAN: I was going to say, as Andrea knows, one of the things that we are thinking about is actually showing the five sectors separately: showing most of the slides that you just saw, which is the big five pieces, and then each of the five pieces, and then finally the thing together. It sounds like you might even be talking about something at a slightly different level. We want to make it easier for the target audiences to comprehend this, yes, not just showing the one big complicated diagram.

DR. FERREIRA-GONZALEZ: I appreciate your comment. I think the value of this type of granular system is to show where some of the gaps are located. If you go to a higher level, you might lose some of that appreciation. We can take into consideration your comment. Marc wants to make a comment.

DR. WILLIAMS: I just think that we have gotten into the philosophy of everything has to be on a one-page executive summary. When we try and distill down horribly complex issues into something that is so simplistic, it really doesn't represent reality and it gives people a false sense of security.

I think the issue more is less the map but more the engagement of actually walking through the map. As I looked at this map and tried to dissect it myself when we were trying to do the review, I found it very confusing. But to have Cliff walk through the different sectors, if you can have that type of engagement, which takes a relatively brief period of time, that is where the real rubber can hit the road.

DR. FERREIRA-GONZALEZ: Steve and then Muin.

DR. TEUTSCH: To Phyllis's point there, I think it is helpful to show here on this map, and we can probably be clearer, where the issues in analytic validity occur and where the clinical utility and clinical validity issues are so at least we can begin to see that where the gaps that we are actually dealing with in the report and trying to fix fit here. It is not like they are in isolated places where you can put your finger directly on them. I think it is important to realize that the problems we are grappling with actually are across the spectrum of this process.

DR. FERREIRA-GONZALEZ: I think that is a very important point. We don't want to lose, for example, that the LDTs go through the FDA and other areas. You need to see the entire picture. But maybe adding, like Marc is saying, the different slides and having them walk through will help whoever is reading this report down the road to understand or actually facilitate the understanding of what we meant by this. Marc.

DR. WILLIAMS: To be responsive to Paul's comment, too, which I think is right on, I think maybe the other thing we could add to this that I don't think would add any more lines [is] we could certainly highlight which parts of the process are currently transparent, i.e. where a sophisticated consumer could actually go in and information, and those parts which are currently behind the curtain. That is a big issue in terms of our research.

DR. FERREIRA-GONZALEZ: Muin.

DR. KHOURY: I just want to build on what Marc said, actually, because this is very, very helpful in our deliberations and discussions later on, especially around the concept of a registry. For any intended use today for any genetic test that is on the market or in this research morass here, or in this winding diagram, for consumers and providers to get the information they need, where would they go. They can go different places.

I think if there is a way, as a starter, to put out all that information together and display it to the stakeholders in a transparent way, that would be a good start in order to inform the providers and the consumers whether or not a test is ready for prime time.

Just by the way of a little correction here, if you look on the right lower corner, "Clinical Utility Review," where you have the U.S. Preventive Services Taskforce and EGAPP, actually EGAPP

was designed not only as just a clinical utility review but to review everything, including analytic validity, clinical validity, of course with an eye towards clinical utility. We have actually used the EGAPP working group, from which there are a couple people here --

DR. FERREIRA-GONZALEZ: So we should put the EGAPP in another place, too.

DR. KHOURY: Right. If there is a way to try to capture this information from multiple places and feed it, whether in a central location or distributed information, that is transparent and accessible to the public through websites, that could actually be a good start to go through this and understand how much of it is downloadable. Right now it looks like an opaque, very thick forest that you are unable to penetrate through.

DR. FERREIRA-GONZALEZ: That is a very good idea. They will have to figure out how to do it. Mara, and then James, and then Gurvanet.

MS. ASPINALL: I would agree on the compliments on this system. I don't believe I have ever seen something as comprehensive as this. First, I would say I think it is important to make the smaller or medium changes so we truly have something that we can put a stake in the ground and say that this accurately reflects the system.

As opposed to the last comments or the related, I think we can use this map with the recommendations. So as we go through the recommendations, we talk about gaps here, but to use this both literally and graphically to be able to say that Recommendation 17 -- I know there aren't 17, but I didn't want to prejudge it -- indeed fills a gap that is G2 over there.

So if this is an organizing principle, let's make sure to use it throughout our whole process.

DR. FERREIRA-GONZALEZ: Paul, you have noticed that you have a single page. Unfortunately, we have a single page, Mara, with the map, but you can still read it. So we will use this, and that is why we have it separate, as we go through the recommendations to go back to this map.

I have James and then Gurvanet, and then I think we are going to try to wrap it up.

DR. EVANS: I would just suggest as a practical issue this overview is so good. When I first looked at this I almost had a tonic-clonic seizure.

[Laughter.]

DR. EVANS: But Cliff's walking through it, which probably took, what, 15 minutes was so good that I would strongly suggest having a very explicit link in the report to that presentation, which I imagine has been captured, because I think that anybody wanting to understand this we should say would be well served by spending the 15 minutes to be taken throughout it by the hand.

DR. FERREIRA-GONZALEZ: Gurvanet.

DR. RANDHAWA: It is a great job, Cliff. I compliment you and your team. This is sort of fine-tuning the map here, but when you look at the upper right-hand and the middle corners, the outcomes research and guideline development is very well laid out but you could consider the same thing happening at the USPS and EGAPP level, where outcomes research information is also used to inform their recommendations.

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Vice versa, in guideline development, the guidelines we are thinking about, clinical utility is a part of their review before making the guidelines. So you may want to consider tweaking that a little bit.

DR. FERREIRA-GONZALEZ: One other thing is that we have here the role of the known regulatory oversight such as the professional guidelines and so forth in the area that we have on the right and middle corners of this slide. Under the DTC, DAT, and clinicians, we have there the professional organizations and other organizations that provide guidelines, but then those actually might have to be also reflected through the CLIA-exempt state and the CLIA regulation because they also apply into how you are actually going to be performing the testing and so forth.

So there is not only the regulation currently but there are also all these other inputs from these other professional organizations or other groups that are providing these guidelines. If there is any way to also put them in these two other main blocks of the CLIA-exempt state regulation and the CLIA regulation.

I think the question we have to ask is does this reflect the charge from the Secretary on a map of the oversight. If you don't think so, please say so.

DR. TUCKSON: Well, I vote that it certainly is responsive with the appended gaps issue, which we will go through, with the only exception that I think that what it misses is a little bit of a commentary on accountability. If we can get a commentary on accountability at the levels of what is there.

Obviously you can't have accountability for the gaps, but assigning the accountabilities of the Secretary's Office in general for driving the overall train and how explicit is that accountability, the accountability for the major government agencies. So, "The head of the FDA is accountable for." Just assigning a rational accountability.

DR. FERREIRA-GONZALEZ: Mara.

MS. ASPINALL: Just briefly, I would very much agree. I think the accountability makes sense. I just want to say on the record it is particularly impressive that you have added the right-hand side that talks about accessibility and reimbursement because that is something that has been an undercurrent in the broadest scope of the industry for a long time and you can't really look at the left-hand side without at least understanding the right.

DR. FERREIRA-GONZALEZ: If you notice, on the map everything is a circle. It is inside a circle.

MS. ASPINALL: It is perfect. Thank you.

DR. FERREIRA-GONZALEZ: We are doing good so far. We will see you later. Now we are going to move to the next presentation.

DR. TUCKSON: Are we done with Rome?

DR. FERREIRA-GONZALEZ: Yes.

DR. TUCKSON: Rome, you are done?

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DR. GOODMAN: Thank you very much. I wanted to just ask our team, Laura and Crystal, to make sure to not let I guess it was Gurvaneet, Steve Gutman, and a few others out of the room without getting their handwritten corrections on their versions of the map to make sure we capture those wonderful suggestions.

We had two rules. One is we had to work in two dimensions. The other one was we couldn't cross lines. That is one of the rules on these things. We will do our best within those constraints, but thank you for the very, very helpful suggestions.

DR. TUCKSON: By the way, because you can't see us, there are 28 of us here who are waiting for the presents from Italy. So, thank you.

[Laughter.]

DR. FERREIRA-GONZALEZ: Cliff, before you leave, I think we need a round of applause. Gurvaneet is asking for that.

[Applause.]

DR. FERREIRA-GONZALEZ: This is going to be a significant contribution to our understanding of this complex issue. Thank you, Cliff.

DR. GOODMAN: Thank you very much, Andrea. Thank you for your leadership in making this map as good as it is so far, and thanks to our team of Laura, Crystal, and others.

DR. FERREIRA-GONZALEZ: Thank you.

DR. GOODMAN: Thank you.

DR. FERREIRA-GONZALEZ: We are going to continue forging through.

DR. TUCKSON: Let me just do a quick check just so we have people's "bladditary" expectations. We are scheduled for lunch at 12:30. We will plow forward and see how we do, and we will see if we can have a natural stop around 12:30. Thanks.

DR. FERREIRA-GONZALEZ: Great.