**Next Generation Sequencing (NGS) Draft Guidances:
Technical and Regulatory Aspects**

**Moderator: Irene Aihie
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Coordinator: Good afternoon and thank you for standing by. All lines are on a listen-only mode until the Question and Answer Segment of today's conference call. At that time, you may press Star followed by the number 1 to ask a question. We will be taking questions via the phone only on today's conference.

Today's conference is being recorded. If you have any objections you may disconnect at this time. I would now like to turn today's conference over to Ms. Irene Aihie. Thank you, you may begin.

Irene Aihie: Thank you. Hello and welcome to today's FDA webinar. I am Irene Aihie of CDRH's Office of Communication in Education. On July 6, 2016, the U.S. Food and Drug Administration issued two draft guidances that when finalized will provide a flexible and streamlined approach to FDA's oversight of next generation sequencing tests.

These two draft guidances support President Obama's Precision Medicine Initiative, PMI, which aims to take advantage of the progress made in genomic testing to accelerate in the development of new treatment that takes

into account individual differences in people's genes, environment, and lifestyle.

The purpose of this webinar is to share information and answer questions about the technical and regulatory aspects of the guidances. Your presenters are David Litwack and Dr. Laura Koontz from the personalized medicine staff here in CDRH.

Following the presentation we will open the lines for your questions related to technical and regulatory aspects of the guidances. Additionally, other center subject matter experts will be joining the Q and A portion of our webinar. Now, I give you David.

David Litwack: All right thank you, Irene and thank you to all, everybody who called in for joining us today to discuss the two guidances on next generation sequencing that FDA published on July 6 of this year.

We will use these webinars to provide more detail on these guidances and particularly here to focus on the technical and regulatory aspects of the guidances and use this opportunity to address questions you may have and clear up things that you may not have understood in the guidances.

So here in this hour we will provide background describing the motivation for release of these guidances and then dive into the details of both guidances.

And then we will discuss what this means for the regulation of next generation sequencing and how we will proceed after these two guidances are finalized sometime in the future, right, and we will provide time for questions at the end of the webinar.

I will discuss the first guidance on the analytical standards for next generation sequencing and then Dr. Koontz will take over and address the guidance on the use of databases.

So first to some background, why did we release these guidances, why did we write them? So as many of you may be aware, President Obama announced the Precision Medicine Initiative in January of 2015.

This effort is designed to enable a new era of medicine through research, technology, and policies that empower patients and providers to work together towards and researchers, toward the development of individualized care.

The center piece of the PMI is really the million person cohort, a PMI cohort program which is going to engage one million participants inresearch that will advance precision medicine.

The PMI also recognizes that the success of research in precision medicine and as translation to the clinic, relies on diagnostic tests that are safe and innovative. And probably no diagnostic test has been more central to the advance of precision medicine than the tests that use next generation sequencing or NGS.

So we've recognized that NGS has unique features that makes it in many ways different than other diagnostic tests. For this reason, as part of the PMI, FDA proposed to optimize its regulatory oversight of NGS tests by developing an approach that takes these unique features into account.

The goal of doing this is to help assure that NGS tests provide accurate and clinically meaningful results and to (unintelligible) innovation and genomic testing. We believe these two goals are intimately linked and the successful

innovation depends on accurate and reliable tests and that appropriately designed oversight in this space can achieve both goals simultaneously.

We have previously discussed the reasons for our proposals and the concepts, and outlined the proposed approach in series of white papers and workshops and you can find these discussions on FDA's website.

In this webinar, I will give you just a brief overview of the goal of the optimized approach before diving into the details of the two guidances.

So conventional diagnostic tests are typically based on science or technology that has come to some sort of answer that is in some sense settled and has been investigated and sort of locked down before coming into the clinic in many senses.

And although there can still be improvements and advances in those technologies and in that science, they tend to happen more discreetly with varying intervals of time marked by stasis.

FDA system of premarket review is well suited to this and has a long track record of success spanning over 40 years. This system has also accommodated those individual NGS tests that have already been reviewed by FDA.

As a class however, NGS is still undergoing rapid technological evolution and the evidence supporting the clinical use of these tests is also rapidly changing. This essentially reflects the state of the field of precision medicine and the fact that as a whole, is undergoing rapid development.

So for this reason, FDA believes that premarket submission and review for each test, and each test modification and each change in evidence that would

necessitate maybe a change in the variants a test is reported to detect would not keep pace with innovation.

Instead, FDA proposed a system as part of the PMI that would be more responsive to rapid changes in the field of precision medicine. The draft guidances published this year are a critical first step in the development of such a system.

Any different approach though must guarantee the same assurances that are provided by FDA premarket review. An FDA review of any IVD typically focuses on three elements.

The first is analytical validity, does the test accurately detect the intended analyte and for a NGS test does it detect the variant when one is present and not detect the variant when it is not present? And this is typically demonstrated by bench testing with the data typically provided to FDA by a test developer or sponsor.

The second is clinical validity, i.e. when you detect the intended (analyte) or (analytes), are you correctly identifying the disease condition, or state of health?
And in NGS, this is often related to the clinical interpretation or the classification as a variant. For IVDs, demonstrating this does not usually require randomized critical trials but instead clinical validity is typically demonstrated by literature, retrospective studies, or other sources of evidence.

Finally, FDA is looking at labeling or what claims are made about the test, because labeling has to be truthful and not misleading and should reflect the analytical and clinical evidence the performance of the test.

Now all of these elements are reviewed in light of the intended use of the test so for instance an NGS test intended to detect circulating DNA may require a

higher sensitivity than an NGS test intended to detect variants to diagnose hereditary disorders.

And thus the bar for analytical validity might be separate in those two cases even though the core technology might be very similar. All right, so given that background, now let's move to the first of the two guidances w which focuses on the analytical standards and how they might be used in the review and oversight of NGS tests.

I should say before I go that taking together these two draft guidances are designed to anticipate and support the needs of rapidly evolving NGS technologies. We want FDA regulation or oversight that can support reliable accurate and understandable test results while promoting an efficient after market for all test developers.

So again, the first guidance describes how standards can assure test quality, describes a potential regulatory path for certain uses of NGS, and the second guidance discusses how FDA and test developers could leverage third party genetic databases to support the clinical validity of genetic variants.

Both of these guidances rest on the foundation of transparency that NGS test performance and the evidence supporting the clinical interpretation of genetic variants should be available to users of these tests.

It's important to point out that these draft guidances are proposals released for public comment. They are not finalized and they do not imply any current requirement that anybody must meet. Nothing has changed at this point in time.

I also want to note that both proposals when finalized describe voluntary paths. We intend for this, these to be alternatives to premarket review. It will

be up to test developers to select the option - premarket review or the so-called PMI path - that best meets their needs.

Ffinally because these are draft guidances, we critically depend on your public comment and we will, there will be many opportunities.We've opened dockets and we'll have links to those dockets at the end of this presentation.

Okay now on to the draft guidance which is the use of standards and FDA regulatory oversight of NGS based IVDs used for diagnosing germline diseases.

One of the first issues we had to grapple with --and I would like to point out that, even before I get to the scope of the guidance, this guidance as well as the database guidance were drafted after extensive interaction with public, with experts, with people who use these tests, who develop them and who run them.

One of the things we observed during that process - many, much variation in how tests were used and one of our goals here was to accommodate that variation. One of the first issues we had to grapple with is how to think about different uses of NGS because it is used for such a wide range of purposes, diagnoses, risk protection, health and lifestyle, targeting treatment and so on.

And when used for diagnosis even for a single use, a broad use like diagnosis, there were still a wide range of tests - those for diagnosing specific diseases like cystic fibrosis, those that diagnose conditions like hearing loss to identify which variant may be causing that, and those are unbiased searches for the causes of disease related to a constellation of symptoms for our purposes. Itt made sense (unintelligible) by a single standard and we ended up binning tests into broad intended uses and this slide depicts some of these bins.

The guidance, this first draft guidance focuses only on one bin, the one titledhereditary disorders and we have done this because of the complexity of trying to address all uses at once. Also because we believe that most of the indications within this bin are moderate risk and that it is , in many ways, technically the simplest case, we believe that this is the appropriate starting point.

(Unintelligible)The guidance applies specifically and as stated in the guidance only to targeted or whole exome sequencing NGS based tests intended to aid in the diagnosis and individuals with suspected germline diseases or other germline conditions.

Throughout the rest of this webinar, when I, in this section referring to this guidance, where I'm referring to an NGS test, whether or not I say it I will be meaning to refer it NGS tests that fall within this broad use.

Know however that in the future we will be expanding this approach to other intended uses and it is a high priority for us to do that, t to cover oncology, liquid biopsy disease risk and all of these other uses.

Okay so the technical recommendations that we provide in this guidance describe an approach to test design. This is done to accommodate different test designs, components, indications, and so on, again, given the wide degree of variability in running NGS tests. We believe it is important for us to preserve that feature as we believe it's important for innovation. The technical recommendations that we provide can form the basis for future FDA recognized standards or special controls and I'll get into that a little later.

So the overall approach that we propose is - they aren't standards at this point but essentially what we're calling design standards or design recommendations or considerations.

The idea here is, again, this is a process of test development. It is not meant to specify specific components or, largely, specific performance characteristics although there are a few exceptions to that.

The idea is to first, in designing the test, identify the intended use and your user needs and use that to set performance, identify performance metrics that the test must meet that are required for that intended use and to identify performance thresholds that that test must meet for each of those metrics.

Once you've identified the necessary performance and this also includes the sort of test run quality metrics we see in NGS that identify whether individual runs may or may not be accepted. This could include things like coverage. We'll get into that, again, a little bit later.

You then actually assemble the test, put the components together, write the SOPs and then you validate to determine whether that test actually meets the predefined performance thresholds.

If it doesn't, you have to modify so you go back to the beginning with test design and repeat until you have designed a test that actually meets the required performance and hence can perform according to its intended use.

Okay so test design - the first thing you do is identify your intended use. Are you going to be testing for undiagnosed diseases in general? Will it be for hearing loss? Will it be for cystic fibrosis?

We also separate out user needs because sometimes there are needs that will affect test design that wouldn't be part of a traditional intended use.

For instance, you may be receiving samples that may undergo extreme conditions under shipping and your test must be able to accommodate those or you may have a certain turnaround time. It may not be in part of your intended use but that still is going to factor into test design.

Specimens - you must identify what specimens you expect to be testing and also for genomics, for NGS tests, what are the interrogated regions? What part of the genome are you going to be sequencing? Will it be specific genes, specific parts of genes, whole exomes, that all must be defined.

From there, you set, again, your performance needs, what sort of accuracy might you need, what sort of precision, and then you move on to identifying the components and metrics you need to get to design a test that meets that performance.

Now all this feeds back - sometimes, for instance, you may be limited in your available components and that may affect the types of uses you can have. It may be that certain sequencers have certain error profiles that prevent you from reliably detecting certain variants.

And so that may -if test components and methods are a limitation, that may affect how you, design the use of your test. So if we drew all the arrows, this would be a confusing diagram but this is an example of how in many cases one of these bins may influence what happens in another bin and this is very much a reciprocal process.

So the test performance - let's provide a little more detail about that. So what we're talking about here is again, identifying performance metrics and setting minimally acceptable thresholds.

The guidance specifies four overall performance metrics that we believe should always be assessed, accuracy, precision, so this is reproducibility and repeatability, limit of detection, and analytical specificity.

And I want to call out here this analytical specificity includes cross reactivity which we know is an issue with, for example, pseudogenes, the reason why some regions are difficult to sequence, as well as cross contamination between patient samples and the ability to detect that.

In some cases, we recommend minimum performance thresholds, but not in most. We believe that a minimum accuracy - the accuracy limits can be set higher but they should be at least 99.9% and the confidence interval around that should be reported, and that a precision of no less 95% should be obtained.

In many other cases though we aren't going to set a value and that's one that a test developer would have to select and document the justification for that. Test run quality metrics - so as I said, these are metrics that assess whether a test run or variant call should be accepted on a run by run basis. And we recognize that different test developers use different metrics and/or even the same metrics for different purposes.
And so we specify coverage as the one metric that developers should always use in some fashion but, there are other metrics that we discuss that can be selected by test developers as the need arises - for specimen quality, DNA quality and processing, sequence generation, base calling, and other types of metrics, but those should be selected and justified --the metrics that should be used should provide assurances that technically, that a test run can be accepted or confidence that a variant call is correct.

General recommendations for performance and evaluation studies - once you've identified your performance metrics from the threshold, and you put

your test together, you have to give validation experiments and we define many elements that should always be included in validation experiments.

Some of the ones I want to stress here are evaluating end to end performance and just not a part of the test, validating across representative genomic regions, variant types, etcetera, that are relevant to your indication, identifying the types of sequence variants - the limitations of the test, what can you not detect with adequate accuracy and precision, and using appropriate specimen types in your validation studies and where you use (unintelligible) or synthetic constructs performing commutability studies to assure those are going to give you adequate validation results.

We don't specify the number of specimens required for validation experiments because that's going to vary in each situation but test developers have to be able to determine confidently the number of specimens required for validation experiments.

So accuracy studies - I just want to make a point that it's important to have a comparator method. Sometimes it's Sangersequencing, sometimes it might be something else.

And in some cases, you can also do a, in the absence of a comparative method, you can also use a comparison to test generated - compare a test generated sequence to consensus sequence of agreed upon well characterized samples. And Genome in a Bottle NA12878 would be an example.

We expect that all results would be - validation studies would be documented with confidence intervals, not just point estimates and broken down by variants, sequence context, and other variables.

Other recommendations are listed in the guidance. We have other recommendations and I won't go into detail, - the use of supplemental procedures like (unintelligible) methodical compensation Sanger confirmation, which may affect how validation is conducted.

But they aren't really considered part of the core process of the test and we discussed those but it is up to the test 'developer's discretion whether that would be sort of part of the test process or not. Variant annotation and filtering, presentation of test performance and test reports and modifications as well. Wee do want these standards to encompass modifications.

Regulatory considerations - so we, in addition to the technical recommendations that we put forward, we also describe, essentially, regulatory paths.And we describe the regulatory path that we think will get us to begin to achieve the overall PMI vision that we've laid out, which would be a standards spaced approach for assuring analytical validity.

So currently, we have a system of classification for IVDs with Class 3 being the highest risk tests that require premarket approval. Currently NGS based tests are Class 3 by default because we have never cleared or approved NGS based tests for the intended use we are discussing here.

However, we believe currently it may be possible to classify these tests as Class 2 devices and we outline what FDA believes is needed to support this classification and we discuss the possibility - to go a step further - that in the future we could even exempt these tests from premarket review.

And this is a process we have used in the past for other IVDs. So the general need here to be able to do this, to get to Class 2 is to obtain a de novo submission. And the de novo pathway is one that allows - it's a type of

submission to FDA that allows FDA to review and down classify, if appropriate, a new type of technology, a new type of test.

In this case, we believe and state in the guidance , (unintelligible) that if we receive a de novo for this intended use we could come to a class two classification decision in which case the technical recommendations that we present could act as special controls. Special controls are just special requirements that a test would have to meet and so those special controls we could, we could do it that way. Now we could also come to a decision that future tests would not even need - would have to comply with the special controls but not even have to come into FDA with a premarket notification.

We would need evidence, justification for that but that's something that could be done in the context of a de novo at some point. And that would allow us to implement standards whether in special controls or through FDA recognized standards that could be based on these technical recommendations without without premarket submission.

So with that, I will leave it and hand it over to the, to Dr. Koontz to discuss the database guidance.

Laura Koontz: Thanks, David. I realize we're hearing people are having trouble accessing the slides and we're working on figuring out that issue is but the slides will be available along with the recording next week, so I apologize for that.

So anyways, my name is Laura Koontz and I'm a member of the personalized medicine staff in the Office of In Vitro Diagnostic here at FDA and I'll now spend a few minutes discussing our second draft guidance document, the Use of Public Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing Based In Vitro Diagnostics.

The guidance outlines the agency's thinking about how genetic databases can be used for the regulatory review of NGS based tests. That is, how public genetic databases that follows certain quality specification can be sources of valid scientific evidence to support the clinical validity of NGS based tests.

So how does the ability to tap into publicly available genetic databases to support clinical claims benefit patients? Databases of genetic variance have the potential to speed evidence development for NGS based tests since the evidence houses these databases is typically generated by multiple parties.

Collectively, we can obtain evidence for the clinical interpretation of a greater portion of the genome than we can individually. Crowd sourcing evidence generation in this way eases the burden on any single test developer and could speed new tests to market.

Importantly, aggregated data could also provide a stronger evidence based for NGS based tests. Tests that use these databases will be connected with the current state of scientific knowledge regarding genetic variance and its relationship to a disease orcondition.

Finally, FDA believes that as more evidence is gathered and improves, new assertions supported by the evidence within the database could be made. Next I'd like to take a minute to outline the guidance before we dive into some of the specifics.

To allow NGS based test developers to leverage these databases, FDA has published this draft guidance which lays out how genetic variant databases can be used as sources of valid scientific evidence to support the regulatory review of NGS based tests.

Specifically the database guidance lays out a series of recommendations that FDA believes, when followed, would allow the database to be considered a source of valid scientific evidence, which can then support the clinical validity of a test.

Database administrators that run databases that meet these recommendations could voluntarily apply for FDA recognition. And I just want to stress again voluntary.

They would then submit an application to the FDA demonstrating that their database meets these recommendations set forth in the guidance. We will discuss these recommendations in greater detail in a minute but broadly they rest upon three pillars.

1. Transparency; 2. , validated processes and formal procedures; and 3. expert interpretation. Lastly, I want to note that because transparency is a key component of these recommendations, the guidance document only applies to publically accessible databases, not proprietary databases.

I would now like to discuss our quality recommendations in the FDA recognition process. Because databases must demonstrate the quality recommendations have been met in their application, I will just discuss the recommendations and the context of an application for FDA recognition of the database.

To become recognized by the FDA, the database administrator would have to demonstrate that the recommendations have been met. This recognition would occur in three steps, first, the database would submit a voluntary application to the FDA for recognition and that is at the discretion of the database administrator.

FDA is not compelling any database to seek recognition and this process is purely voluntary. Second, the FDA would assess the genetic variant database's policies and procedures for obtaining and maintaining data and making variant assertions.

This would include evaluating the database to ensure that it provides transparency regarding its data sources and operations including versioning and use of publically accessible SOPs or standards operating procedures.

That it provides sufficient assurances regarding quality of the source data including the use of accepted nomenclature and clear documentation of the evidence used to make variant assertions, that it has SOPs that define how variant information is aggregated, curated, and interpreted, and further that the SOPs outline how assertions about a variant are made are based on validated decision matrices.

That data is collected, stored, and reported in compliance with all applicable regulatory requirements regarding protected health information, patient privacy, research subject protections, and data security and that variant assertions are made by qualified experts and these experts adhere to the database's conflict of interest policy and that they disclose any conflicts.

It's worth pointing out that this is an incomplete list of recommendations and there are additional details and recommendations in the guidance. And then finally as part of recognition process, FDA may spot check variant assertions to assure to they're made in accordance with the database's SOPs and reflect the current state of scientific knowledge.

Now once the database has been recognized, the third step is maintenance of that database's recognition. This maintenance of recognition would occur through periodic reassessment of the database's SOPs and its assertions.

So once the database has been recognized, FDA believes that the evidence contained in that database would generally constitute valid scientific evidence that could be used to support the clinical validity of next generation sequencing based tests.

The assertion that a database could make a genetic variant include a variety of different variant types, such as relating to the pathogenicity of a variant or whether that variant may be related to a certain response to therapy.

At our public workshops we heard that it was important for patients and providers to receive information regarding variants of uncertain significance as this may be medically useful information for an individual patient.

Therefore we have proposed that it would be permissible to report this type of information but we'd like to receive public input on that point. Regardless of the type, all variant assertion should be supported by adequate information detailing the evidence within a genetic database supporting that assertion.

For example, how many times has a variant been seen in people with a certain disease or condition, what scientific data linked a gene to a disease and what is the biochemical nature of a variant effect on the encoded protein and so on.

Those assertions should also be an accurate reflection of the current state of scientific knowledge and generally would integrate multiple lines of evidence. And finally all assertions should not be false or misleading.

We believe that these recommendations dovetail with the recommendations regarding test reports in the analytical standards guidance that David mentioned. Those recommendations state that, among other things, the relationship between a reported variant and a clinical disease recognition being assessed must be clearly stated.

In summary, this guidance document outlines an approach that allows test developers to take advantage of the benefits of data aggregated in FDA recognized databases to support the regulatory review of their test and it outlines a pathway for databases to voluntary seek recognitions.

Next, I'd like summarize the two guidances and discuss those future implications.

Taken together, these databases, these excuse me, these guidances discuss the possible future down classification and exemption from premarket review of NGS based tests that can demonstrate conformity with the standards outlined in the analytical guidance and use assertions from FDA recognized databases.

FDA believes that this potential approach offers speed, scalability, and safety. So speed, this approach when finalized would provide test developers with an efficient path to market and connect patients with tests quickly.

Scalability, test developers both large and small can benefit from this approach because it is based on standards and evidence that everyone can access.

And safety. That this approach encourages innovation while still assuring patients and healthcare providers that NGS based tests are safe and effective and that they provide accurate and meaningful results.

So next steps. Currently the draft guidance documents are open for public comment until October 6. During the public comment period, we also plan to hold a workshop to discuss the guidances and that will occur later this fall and we hope to be able to announce that date soon so keep your eyes peeled for that.

Following closure of the open comment period, we will of course analyze comments, make any necessary changes, and hopefully move towards finalization and implementation.

Eventually, we also hope to expand this approach to other intended uses of NGS based tests, such as for oncology, and will have opportunities for the community to comment on additional standards or criteria that would be necessary to assure the safety and effectiveness of these other types of NGS based tests.

And so as I mentioned, the comment period for each of these guidance's open now through October 6. We hope that you will submit comments regarding the substance of each of these guidances, what we got right, what we didn't, what you think we should change.

Each of these guidances is also accompanied by a federal register notice and includes specific areas that the FDA is seeking public comment on in addition to whatever else you'd like to comment on.

And so as you are developing your comment, I encourage you to look at these questions and offer your feedback on them. And then finally before we get to the Q and A portion, I'd like to put in a plug for additional ways that you can be part of the process.

To fully realize the vision outlined in these draft guidances and expand it to other indications in the future, we need your help. We need community input on the technical recommendations of potential standards for the uses like oncology and standard developing organizations to issue consensus standards for NGS tests.

Following our involvement in the creation of the genome in a bottle reference genome, FDA continues to work on a creation of reference materials in partnership with other public and private institutions, organizations.

FDA encourages community aggregation of genetic variant information and supports data sharing efforts necessary for the creation and continuation of sustainable high quality databases and finally curation.

As we've heard at all of our public workshops that databases are dependent upon external experts to assisting in curation and interpretation activities and there's always more work to do. So please consider getting involved too and now I'm happy to turn it back over to Irene.

Irene Aihie: Thank you. We'll now take questions.

Coordinator: Thank you. At this time, if you do have any questions or comments, you may press Star followed by the number 1. Again, that is Star 1 to ask a question and Star 2 to withdraw your question. (Carol Ryerson), you may ask your question.

(Carol Ryerson): I was looking for information on accessing the slides since they weren't available to us during the presentation so I think that was addressed that we'll be able to access them on the website in a week.

Irene Aihie: No - hi, my apologize. You can actually access them now on CDRH Learn. We have a slide, well, I'll go ahead and read the address for you. We apologize again. That is www.FDA.gov/training/cdrhlearn and when you get to that page, you can actually find the slides under the heading Specialty Technical Topics and the subsection Device Specific Topics.

Again, we do apologize for participants not being able to access the slides via MyMeetings.

Coordinator: We do have a few more questions. (Laura Lee), you may ask your question.

(Laura Lee): Hi this is a question for Dr. Litwack. It's more of a clarification question to a statement that you had made. You had said that when final, the analytical standards NGS guidance is intended to be an alternative to premarket review for NGS test developers and they can decide to follow traditional premarket review or the PMI path.

So my question is does that mean if the test developer followed the design standard with it in the draft guidance once it becomes final, does that not, no longer include the QSR requirements for design control, et cetera?

David Litwack: We expect that the general controls including QSR would still apply in any situations. These are meant to sort of be the equivalent of special controls you know, to guarantee analytical validity.

(Laura Lee): Okay thank you.

Coordinator: Thank you. Our next question comes from (Ash Car). You may go ahead.

(Ash Car): Hi. Thank you for taking my question and your presenting this emerging topic. I would like to (unintelligible) recognized databases? Thank you.

Laura Koontz: I'm sorry I think you broke up a little bit. Could you try to repeat the question?

(Ash Car): Sure. My question is (unintelligible) a list of FDA recognized databases?

Laura Koontz: I think the question was where can you access a list of FDA recognized databases. At this time, there are no FDA recognized databases. With the draft guidance, we hope to move towards finalization and have databases come in to be recognized.

That process again is voluntary so it would be at the discretion of a database wishing to come in and be recognized but no, at this time there are no recognized databases. At the time that we do recognize them, we'll put them on our website and make sure that that information is available to everybody.

(Ash Car): Okay thank you.

Coordinator: Thank you. (Laura Bean), you may ask your question.

(Laura Bean): Hi, I have two questions. The first is do you plan to provide laboratories with the template for submitting this information? And then secondly in regards to databases, once you have an approved recognized database, how are you viewing the assertions that are in that database?

Is this, are you using this information that may be helpful to a laboratory or are wiling assertions which may change overtime as more information becomes available? Are you viewing this as the appropriate assertion for variant?

Liz Mansfield: Hi, this is (Liz Mansfield). I'm the Deputy Office Director for Personalized Medicine here and at this time, we don't anticipate supplying a template because it's not clear to us that a template would be appropriate for this.

The people may address the standards in different ways and usually an opportunity to address standards in different ways and there's an opportunity to deviate from the standards with appropriate specifications.

So generally we don't use templates although if you would like us to, I would certainly encourage you to include that in comments and perhaps provide some more details if you can. The second question…

Woman: In this case, if people are submitting their groups of genes or it's variations on the same test (unintelligible) same basic data with different gene lists, then it may be appropriate in this case.

Liz Mansfield: Okay. And the second questions was about how we view the assertions and the database. We expect the databases that when they're used for, to support clinical validity claims will be (unintelligible) so we will know at what point do you reference that database and can refer the assertion at that date.

We do expect that people would be able to update their assertions based on changes in the databases. In general, we hope that we can find a way for that to be done without returning to FDA for any kind of clearance or approval so it would just be, it would be an ability to update sort of in real time.

Coordinator: And would you like to go to the next question?

Irene Aihie: Yes, please.

Coordinator: (Karen) (unintelligible) may ask her question.

Man: Oh, sorry. I think you're referring to (Karen) (unintelligible) from (unintelligible) Oncology?

Coordinator: Yes, your line is, your line is open.

Man: Hello? I'm sorry. This is a colleague of hers. So I'm asking when you expect to have a draft guidance for tumor sequencing?

David Litwack: We can't, I couldn't project a specific date but I would, we would like to do is see the public comment that we receive on this because we think this would form the core of any recommendations for tumor sequencing or other oncology related applications.

And then I think it's definitely, it's one of our priorities to then extend this to a somatics so we hope it will be one of the next things we can do but you know, we want to wait and see what the comments are on this sort of simpler case.

We recognize that for somatic mutations, there are special technical considerations that we have to build into this.

Man: Great thank you.

Coordinator: Thank you. (Laura Lee) you may ask your question.

(Laura Lee): Hi. I have a question on the previous presentation. I think it's great that this guidance document is getting out. Regarding the four metrics that is, accuracy, precision, (unintelligible), cross contamination and cross activity, more

specific guidelines expected it to come out in view of different operation types and so on.

Woman: So we have a little difficulty hearing you but I think your questions was do we expect to put out additional guidances based on, with more specific information based on different types of genomic varience?

(Laura Lee): Yes, yes this is (unintelligible) metrics that were laid out in the previous presentation, precision, accuracy (unintelligible) and cross contamination (unintelligible).

Woman: What we're really hoping will happen is that the community will develop standards that address these various areas. If it's something that's critical to your test and the way that you're running your test and the intended use of your test then we would in general expect that you would address it in some way.

I don't believe that we plan on putting out additional guidances at this time.

David Litwack: So let me also follow up and say if there's specific information you believe we ought to provide, we would like to receive that in public comment.

(Laura Lee): Got it. Thank you.

Man: Thank you.

Coordinator: Thank you. (Elise Cuban), you may ask your question.

(Elise Cuban): Hi so my question is for Dr. Litwack. So I think someone might have alluded to what I'm going to ask but I was looking at the draft guidance and I was just

wondering specifically why the current draft guidance is designed such that it's mostly for like, standalone diagnostic purposes and doesn't necessarily include any screening or potential tumor genome sequencing.

And I just wanted to get some clarification of why that was the case if possibility that maybe in the near future a draft guidance would be developed for that particular purpose.

David Litwack: That's a good question and something we considered very carefully. I think the reasons were really twofold. One is, and I should qualify that this isn't really, if you read the intended use of (unintelligible) it's not really for standalone diagnostic purposes, this is an aid in diagnoses.

So, but that's something we also hope to get comments on during the public comment phase but we chose this for two reasons. One is we believe that most of the uses are moderate risk.

And that provides us with certain you know, that allows us to you know, we think that's, we would rather develop this based started with lower risk, relatively lower risk uses of NGS and then extend to the higher risk uses of which we would consider or say oncology's somatic, variant testing higher risk.

The second reason is that technically we view this as probably one of the simplest cases. So again, we felt like this was sort of the core you know, recommendations that would probably be true for most tests, but then if we move to something like somatic, we have special issues of sensitivity for instance that we need to consider.

And so we thought it would be valuable at this point to put this out, get comments on it while we are developing the you know, the specialized recommendations for say, somatic testing or for risk or something like that.

So it's not that we don't intend to do it and we would like to cover it, it was just a sort of practical decision in many ways.

Coordinator: Thank you. Once again, if you would like to ask a question, you may press Star followed by the number 1. (Lee Lye), you may ask your question.

(Lee Lye): Thanks. Hi, this is (Lee Lye) from (unintelligible). Thanks very much for giving me the opportunity to ask questions. I have two questions here.

My first question is that I know the guidance, draft guidance (unintelligible) saying it covers whole (unintelligible) sequencing and cognitive (unintelligible) but I'm just wondering about whole genome sequencing, using whole genome sequencing to do the diagnoses. Was there anything that would (unintelligible) the guidance? (unintelligible).

David Litwack: Well we intentionally separated that whole genome for now just because it's, you know, it's slightly different in terms of its design. It's not that we don't want to encompass whole genome, but we wanted to again, get comments on this more limited use before we start tackling any variation.

And I think that was, that was the reason but we fully intend to expand to whole genome you know, even though it's probably not as widely practiced as targeted panels or whole exome now. It's something I think we could very well anticipate in the future and is going to be more as the cost drop and things get easier, it's going to be used more and more.

(Lee Lye): Thanks. And I have a second question. So there's one of the slides that you've listed you know, different categories of these tests and that will in the future, we're looking for standards and guidance on guidance.

(unintelligible) more towards direct consumer selling or is that considered as a medical kind of you know, (unintelligible) requirement as the (unintelligible) area?

David Litwack: I think, it was a little difficult to understand your question but were you asking, if you were asking whether this extends to (unintelligible) testing, direct to consumer testing or whether we intend to do that.

(Lee Lye): On slide 13, you have (unintelligible) scope of (unintelligible). One of the (unintelligible). So my question is that is the (unintelligible) considered as a medical (unintelligible).

David Litwack: Oh lifestyle I see. I'm sorry, it was very, it was difficult to understand you but I think that yes, so lifestyle you know, it's difficult and something we hope to get comments on you know.

But I do think that you know, that it's certainly a use that is claimed for genomic, genetics and genomics and I think you know, right now I mean, I would condemn that there were some medical implication to that even if they intend us to limited to health and wellness or lifestyle.

So that's something we consider more and I think we will you know, welcome comments on that, you know, we recognize there are going be fuzzy borders around these bins you know, and it can be difficult too.

(Lee Lye): Thank you.

Coordinator: Thank you. And our last question comes from (Nate Carrington). You may go ahead.

(Nate Carrington): Yes I have a quick question about the modification section of the guidance. So currently the modification section does not reference the K97 modification guidance for deciding when to submit a 510K for a currently cleared device.

It also doesn't reference the PMA supplemental process so I was curious if not referencing those aspects was intentional and what your thoughts were on that.

Liz Mansfield: Hi, this is Liz Mansfield. These two guidances were intended to lay out proposals for how we might look at analytical validity and how database could be used as sources of valid scientific evidence. They are not intended to lay out all of the regulatory issues and requirements around making a submission for a particular product and updating that product over time.

So did we leave out it intentionally? Yes because we weren't, didn't really want to go into this discussion of every possible regulatory issue with tests but it doesn't mean anything about the K97 guidance.

(Nate Carrington): Thank you.

Coordinator: Thank you. At this time I would like to turn the call back over to Irene Aihie.

Irene Aihie: Thank you. This is Irene Aihie and we do appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on CDRH Learn webpage at www.fda.gov/training/cdrhlearn by Thursday, August 4.

If you have additional questions about the draft guidance, please use the contact information provided at the end of the slide presentation. As always, we appreciate your feedback. Again, thank you for participating and this concludes today's webinar.

Coordinator: Thank you for joining to today's conference call. You may go ahead and disconnect at this time.

END