FDA NGS Webinar

Moderator: Irene Aihie
May 24, 2018
2:00 pm ET

Coordinator: Welcome and thank you for standing by. All lines have been placed in listen-only mode until the question and answer session at the end of today's presentation. To ask a question, please press star one on your touch tone phone.

Today's call is being recorded. If anyone has any objections, you may disconnect at this time. I would now like to turn the call over to Irene Aihie. Thank you, you may begin.

Irene Aihie: Hello. And welcome to today's FDA webinar. I am Irene Aihie, of CDRH's Office of Communication and Education. On April 13, the FDA issued two final guidances related to precision medicine.

The first guidance -- titled Considerations for Design, Development, and Analytical Validation of Next-Generation Sequencing-Based In-Vitro Diagnostics Intended to Aid in the Diagnosis of Suspected Germline Diseases -- provides recommendations for designing, developing, and validating NGS-based tests used to diagnose individuals with suspected genetic diseases.

The second guidance -- titled Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In-Vitro Diagnostics -- described an approach where the test developers may rely on clinical evidence from FDA-recognized public databases to support clinical claims for those tests and provide assurance of the accurate clinical evaluation of genomic test results.

Today Adam Berger, Zivana Tezak, and Laura Koontz will discuss and answer questions about the final guidances. Following the presentation, we will open the lines for your questions related to information provided during the presentations. Now I give you Adam.

Dr. Adam Berger: Thank you Irene. And thanks to all of you for joining us today. My name is Dr. Adam Berger and I am part of the Personalized Medicine Staff here at FDA. As Irene mentioned I'm joined today by my colleagues, Dr. Zivana Tezak and Dr. Laura Koontz, also of the Personalized Medicine staff and we will be discussing the two next generation sequencing guidances that were finalized on April 13 of 2018. In terms of an agenda for today's webinar, we will be going over the background for why FDA has developed these guidances as well as highlighting the major differences between the draft versions and the final versions.

And -- as Irene mentioned -- at the end of the presentation we will go ahead and take any questions you might have. So, we'll go ahead and start with the background for why FDA developed these guidances and what are the agency's goals in doing so.

Precision medicine is an approach to disease treatment and prevention that takes into account individual variability in lifestyle, environment, and genes with a focus on getting the right treatment to the right person at the right time.

New technologies have been developed over the last several years that have enabled greater identification of these characteristics, including in genome sequencing with the advent of next-generation sequencing -- or NGS.

NGS itself is a technology that can rapidly and cheaply determine nearly the entire sequence of an individual's genome. This technology plays a critical role in advancing precision medicine precisely because of its unprecedented ability to identify that individual variation. However, NGS presents challenges for our traditional regulatory paradigm.

In traditional testing -- where one test yields one result -- FDA would require validation of the analyte that the test detected. However, with NGS, one test can provide volumes of data, which often in the germline space cannot be predefined or the disease identified until after the test is actually performed.

The agency recognizes that requiring validation of each variant that could potentially be detected can be infeasible when this can be up to millions of variants. Regulating these tests in a way that enables innovation required us to develop a nimble regulatory approach that could keep pace with the technological and scientific advancements in the field.

Our vision was to implement new regulatory policies that promote research and accelerate the translation of precision medicine technologies into treatments that benefit patients. Overall we are trying to provide clarity to and an efficient path to market for these technologies while making sure that patients receive accurate and meaningful information.

In developing this regulatory approach, FDA sought to engage the public. We held five workshops -- from 2015 to 2016 -- to garner input on the overall

vision and technical details for analytical performance and clinical interpretation and to understand patient and provider perspectives.

Some of the key things we heard from the public were that analytical standards should be a combination of design processes and performance standards; that there's a need for clarity and transparency about a test's performance and its limitations; and that there is a need to incentivize data sharing.

After taking into account the feedback and insight we received from the public, we issued two draft guidances in July of 2016 that described a regulatory pathway for NGS-based tests for certain uses. In doing so FDA was trying to anticipate and support the needs of a rapidly-evolving technology while ensuring that patients - while ensuring patient safety and assuring the quality and reliability of NGS-based tests.

FDA feels that tests developed according to these guidances would be anticipated to have an efficient pathway to market. The draft guidances lay out a two-pronged regulatory strategy for NGS-based IVDs for diagnosing germline diseases.

The first approach details technical standards for NGS-based tests. Test developers that meet these standards may not have to submit a pre-market submission to FDA. We envision that these standards would be developed with the scientific community and can be updated as science and technology advance.

Zivana will go into further detail on these technical standards later in the talk. The second approach outlines a process whereby a public database of human genetic variants could apply for and potentially receive FDA recognition as a

source of valid scientific evidence that test developers may be able to use to support the clinical validation of their test. Laura will delve into the details on this concept later in this webinar as well.

So, moving to the guidances section of the webinar, let's go ahead and dive into the guidance on Design, Development, and Analytical Validation of Next Gen Sequencing-based IVDs. The scope of the draft guidance was specific to targeted or whole exome sequencing NGS-based tests intended to aid in the diagnosis of individuals with suspected germline diseases or other germline conditions.

This scope was clarified in the final document in response to comments that indicate that the guidance only specifically applies to NGS-based tests intended to aid clinicians in the diagnosis of symptomatic individuals with suspected germline diseases.

The draft guidance also laid out recommendations for the design, development, and analytical validation of NGS-based tests that FDA continues to believe could form the basis of future FDA-recognized standards and/or special controls that could reasonably assure the safety and effectiveness of these tests.

The guidance also laid out a potential pathway whereby NGS-based tests intended to aid in the diagnosis of suspected germline diseases could be considered as candidates for down classification to Class II devices, since all novel tests -- including those with the intended use described in the guidance -- are Class III by default.

FDA continues to believe that this may be possible in the future as we gain more experience with these devices and develop special controls that could

provide a reasonable assurance of the safety and effectiveness NGS-based tests intended to aid in the diagnosis of suspected germline disease -- possibly under certain conditions of exemption -- without the need for 510(k) pre-market review.

I've already mentioned that we made revisions to the draft document in response to comments. Overall we received comments on the draft guidance from 38 organizations and individuals.

Commenters were generally supportive of the proposed regulatory approach, and provided comments asking for clarification of the background, scope, and certain technical recommendations, including requests for the removal of specific thresholds for analytical performance. To go ahead and highlight some of the major changes from the draft to final in response to comments received, the title was revised to better reflect the scope and content of the guidance, to acknowledge that currently there are no applicable standards that FDA can recognize, and to support community engagement in developing standards by standards-developing organizations. The scope was clarified as I mentioned earlier.

The analytical performance thresholds that were - that were included in the draft have been removed in the final guidance, which now recommends that test developers pre-define, justify, and report minimum acceptable overall and target threshold metrics such as accuracy, precision, and coverage. Finally, clarifications to accuracy metrics, performance evaluation studies, and other technical recommendations were made in the guidance.

I'm now going to go ahead and turn the presentation over to Dr. Zivana Tezak, who will describe in more detail the analytical validation sections of the final guidance, including further details about the changes I've just highlighted.

Dr. Zivana Tezak: Thank you Adam. Like Adam, I'm very happy to be with you today. And I will now try to take a bit deeper dive into the first of the two final guidances that Adam started to talk about.

So, Adam has already provided a high-level description of the major changes from draft to final guidance. And that was in response to a number of public comments we received after issuing a draft. In the next few slides I will provide an overview of the major sections in the final guidance. And -- as you can see on this slide -- I'm starting with recommendations for design, development, and validation.

Now, this section covers test design, performance characteristics, run quality metrics, and performance evaluation studies. The design section describes the test design approach, starting from the purpose for testing, steps to follow, what is needed, what is available.

You will note that the recommendations on how to design the test are very flexible. They can accommodate different test designs, different indications. Something to pay some attention to are the recommendations on the interrogated regions of the genomes are designed to ensure that test developers can provide transparency in what genes their test can and cannot detect.

Now about the performance characteristics. In the next couple of slides, I will dig a bit deeper into major test performance characteristics since these can be very challenging for NGS tests. Of course, performance characteristics include accuracy, precision, LOD, and analytical specificity.

The bullet point on test run quality metrics. Probably many people on this call are very familiar that this is the very NGS-technology-specific part. So, it's technology-specific in the guidance too. And these quality metrics are useful for assessment whether a test run or variant call should be accepted.

They include metrics such as coverage depth, coverage completeness, as well as select metrics -- for various steps of the test -- such as specimen quality, base calling, or mapping. And -- as in the draft guidance -- ultimately the recommendations outlined in the guidance can form the basis of future FDA-recognized standards or FDA special controls. So - and I will go into performance evaluation studies in the next few slides.

So here I will highlight some parts mentioned on the previous slide. As Adam already mentioned one of the major changes from draft to final guidance is that -- in response to numerous, numerous comments, against providing specific thresholds -- the Test Performance Characteristics section was edited to remove those.

So, we removed these specified minimum numeric thresholds. Instead, the final guidance recommends that test developers pre-define, justify, and report minimum acceptable overall and target threshold metrics. These thresholds will of course depend on technology, indications for use, and different variables such as types of variants that are detected and reported by the test.

We do expect that specific numeric thresholds will be defined and specified in either upcoming consensus standards or special controls developed by the FDA. But those will be appropriate for a specific test or specific indications for use.

The accuracy part. So NGS test accuracy should be calculated for each variant type in the context in which the test can detect them as well as for clinically relevant variants. The accuracy metrics section has added clarity and it's reflecting the importance and definition of metrics such as PPA, NPA, and TPPV.

We have added a new subsection that's illustrating accuracy metrics calculations. And we have also added the appendix in the final guidance, which was a very, very simplified example of such calculations. And that was all added in response to comments that were encouraging us to provide more details and sample tables and templates that demonstrate how to address, present, and calculate different accuracy metrics.

And I will go in the next slide now into performance evaluation studies. So, this section was expanded significantly in response to comments asking for clarification on types of samples and types of studies that can be used to evaluate test performance. And I will mostly highlight the accuracy part.

So, accuracy is generally evaluated by comparison to a method identified as appropriate comparator. And in the past or for sequencing that has been mainly bidirectional sequencing. We have been however accepting other well-validated methods.

For example -- and as appropriate -- accuracy can be evaluated by comparing to the sequence generated by - comparing sequence generated by a new test to a well-characterized -- so called gold standard -- reference sequence or a consensus sequence of agreed-upon well-characterized samples. This will of course depend on the availability of such samples.

Study samples. They should reflect the specimen types tested. And they can include a mix of well-characterized reference samples, they can include clinical samples that are relevant for the test, and appropriate surrogate samples. This section also includes recommendations for when to use in silico samples.

For variant types, it may be helpful to use the results of studies conducted with -- again -- well-characterized reference materials or some agreed-upon samples with high confidence calls. For clinically-relevant variants the accuracy calculation should use the results of studies conducted with clinical samples pertinent to test indications.

As far as the number and type of samples that are required to demonstrate that performance has been met and the thresholds have been met with confidence for relevant metrics and the indications for use. That will depend on, again, indications for use and purpose of the test. And the number and types of variants. What are the number and types of variants claimed to be detected and reported by the test, and the other critical performance parameters that must be met to support that use? Additional sections of the guidance are listed on this slide and include supplemental procedures, variant annotation, filtering, and test labeling. Recommendations for what to present in test labeling include identification of genomic regions, sequence variants, or maybe variant types the test can and cannot detect and report.

If part of an interrogated genomic region is difficult to sequence and cannot meet appropriate performance specifications, this should be reported as a test limitation. So, transparency is very big and important. Test labeling needs to include any limitations of the test.

For example, if the test cannot detect certain genes, certain types of sequence variants, certain allele frequencies, genomic context, certain rearrangements, insertions or deletions that are larger than a certain size or not detecting parts of specific genes relevant for test indications for use.

So, to wrap up with the significance of this guidance. It provides technical recommendations for designing, developing, and validating NGS-based tests for patients basically with either signs and symptoms or suspected of genetic disease. We believe these recommendations if followed can provide a reasonable assurance of the analytical validity of these tests.

We also believe that recommendations in this guidance can be taken on by maybe standard development organizations -- or SDOs -- and that they can form the basis for consensus standards that can be developed by relevant stakeholders and experts. Standards developed by accredited consensus standards bodies are regularly recognized by the FDA.

And of course, the advantage of standards is that they can be updated as technology and knowledge advance. Conformance with FDA-recognized consensus standards can be used to support a reasonable assurance of safety and/or effectiveness for many applicable aspects of these tests, we think.

We envision relying on compliance with FDA-recognized standards that would guide the development and validation of NGS-based tests and can replace some of the pre-market review to provide a reasonable assurance of test validity. Now, in the absence of consensus standards -- or while we are waiting for such standards to be developed by the community -- we can use the recommendations in this guidance as a basis to develop specific special controls. And that can allow the down-classification, potentially, of these tests or even maybe potentially exemption of pre-market purview.

We believe that recommendations in this guidance benefit all types of stakeholders that are involved with NGS. So, test developers we think can have a clear and transparent path to market. And in certain cases, may be even exempt from FDA premarket review. Patients and providers can get faster access to more accurate tests with well-validated, transparent performance. And FDA's mission of protecting and improving public health can be fulfilled in a more streamlined and a more rapid manner.

So, I will now turn the presentation over to Dr. - my colleague Dr. Laura Koontz to go over the database guidance.

Dr. Laura Koontz: Thank you Zivana. So, I will now spend the new few minutes discussing the second of our two final guidances, The Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In-Vitro Diagnostics.

This guidance outlines the agency's thinking about how genetic databases can be use in the regulatory review of these tests. Specifically, how public genetic databases that follow certain quality specifications can be sources of valid scientific evidence to demonstrate clinical validity.

So, first, I want to take just a second to define what we mean by human genetic variant databases. For this guidance, a genetic database is both a collection of assertions about the link between a genetic variant and a disease or condition. The way that these collections are structured can vary and assertions can be things like pathogenic, clinical significant, or even variant of uncertain significance.

Genetic databases are also publicly accessible. By that we mean that the assertions and the underlying data and SOPs used to arrive at those assertions are transparent and available to all users. As a best principle, publicly accessible databases would be open access. But some databases that operate with licensing models for commercial use could also be in scope of this guidance.

So how does the ability to tap into publicly available genetic databases to support clinical claims benefit patients? Databases of genetic variants have the potential to speed evidence development for genomic tests since the evidence housed in these databases is typically generated by many people all over the world.

Collectively, we can obtain evidence for the clinical interpretation of a greater portion of the genome than we can individually. Aggregated data could also provide a stronger evidence base for genetic and genomic based tests than any single test developer could amass on their own.

Tests that use these databases would be connected with the current state of clinical knowledge regarding a genetic variant and its relationship to a disease or condition. Finally, FDA believes that as more evidence is gathered, new assertions could be supported by that evidence and be made by databases.

FDA has been able to leverage databases twice before in our regulatory review of submissions. And I'd like to take just a second to highlight these, but will note that more information about each is available publicly in publicly available decision summaries on our website. First, Illumina was able to leverage the publicly accessible CFTR2 database of Cystic Fibrosis variants in their submission for the MiSeq CF 139 variant assay.

Second, Myriad used their own proprietary database to support the submission of their BRACAnalysis companion diagnostic. Notably, Myriad provided us with the SOPs for how they make assertions about never-before-seen variants. And in doing so, were allowed to report out these new calls to physicians as part of their approval.

These experiences helped the agency formulate and build upon the recommendations laid out in the final guidance, which we will now discuss.

As mentioned, in July 2016 we released the draft guidance with the goal of allowing NGS-based test developers to leverage genetic databases as done in those two submissions. The guidance proposed how genetic variant databases could be used as sources of valid scientific evidence to support the regulatory review of NGS-based tests.
Specifically, the guidance laid 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 support the clinical validity of an NGS-based test.

The draft guidance also proposed that NGS - or that database administrators that run databases that meet these recommendations could voluntarily apply to the FDA for recognition. They would need to submit an application to the FDA demonstrating that their database meets the recommendations set forth in this guidance.

The FDA received over 250 public comments on the draft guidance from 38 different stakeholders spanning the genomic community. We've heard from industry groups, scientific societies, patient advocacy organizations, and others. On the whole, commenters were generally supportive of the proposal

outlined in the draft guidance, but requested that the scope be expanded to incorporate additional uses of genetic variant databases.

While the draft guidance was agnostic in terms of germline versus somatic indications, we heard that commenters wanted it to explicitly include somatic. Commenters also asked for technical clarifications on various points in the guidance, and clarification on the definition of publicly acceptable. FDA took all of these comments into consideration and opted - ultimately opted to expand the scope consistent with stakeholder suggestions and added clarification where necessary.

Next, we will talk about the specific changes we made from draft to final and we'll then summarize the final guidance. As I mentioned, we received numerous comments asking us to expand the scope to encompass all genetic and genomic based tests regardless of technology. For example, tests that rely on PCR or SNPchips should be able to leverage FDA-recognized databases to support their clinical validity.

We agreed. And in the final guidance you will see that we have expanded the scope and the title to reflect this. Regarding publicly - regarding the definition of publicly accessible. As a best practice, we believe that databases should follow an open access model. That is, that the information about an assertion and the evidence underlying is available to anyone at no charge.

We believe this will foster greater accuracy, understanding, and use of these databases. However, databases that use licensing models or charge fees for commercial access -- provided that all of that data is still publicly accessible -- may also fall within the scope of this guidance.

While out of scope of the guidance, proprietary databases -- or ones that charge fees for access -- may also be sources of valid scientific evidence that could be used to support the clinical validity of tests. Test developers that rely on these types of databases may find a database - may find the recommendation within this guidance useful when preparing pre-market submission for those IVDs.

Any database administrator who has questions about whether or not their database is eligible for recognition -- or the evidence within could be relied upon as valid scientific evidence -- is encouraged to contact us.

Also in response to comment, we clarified that somatic variant databases were in-scope for this guidance, and added metadata recommendations for these types of variants. And finally, we expanded details about the voluntary database recognition program, including information on how interested parties can submit information to the FDA to apply. We will discuss this in more detail later in this webinar.

Next, I'd like to take just a couple of minutes to discuss the recommendations from the final guidance. These recommendations are geared towards administrators of the database, not a test developer. Databases that meet the recommendations outlined in this final guidance could be considered a source of valid scientific evidence and could be used to support the clinical validity of tests. These recommendations fall broadly into five different buckets.

The first, transparency. Transparency is the cornerstone of this final guidance document. Because the FDA is proposing to rely upon assertions from databases and review their policies and procedures, but not each individual assertion, transparency is critically important.

Databases should provide transparency regarding its data sources, its operations, and including the use of publicly available SOPs. Further, the SOPs and assertions should be versioned so it's clear to the user not only how an assertion was arrived at, but when it was made, and how it may have changed from previous versions. Finally, data should be presented in standardized formats and the format used should be disclosed.

The second is data quality. Databases should provide sufficient assurances regarding the quality of their source data, including the use of accepted nomenclature and clear documentation of the evidence used to make variant assertions. We would like to see sufficient metadata regarding variant assertion and the underlying data used to make those calls.

Three, SOPs. Databases should have SOPs that define how variants are evaluated in order to arrive at an assertion about that variant's clinical significance, pathogenicity, and so on. Further, the SOPs that outline how those assertions are made should be supported by validation studies.

Four, the use of qualified experts. Variant assertions should be made by a qualified expert. And these experts should adhere to a database's conflict of interest policies and publicly disclose any conflicts. The guidance also discusses the need for adequate training of database personnel and the need for methodology to ensure that individuals undertaking variant evaluation meet and maintain high quality standards over time.

And five -- finally -- database hygiene. Data should be collected, stored, and reported in compliance with all applicable requirements regarding protected health information, patient privacy, research subject protections, and data security. The final guidance does not spell out each of these requirements, as they may differ on a case by case basis, but states that the database

administrator should know which laws and regulations are applicable and follow them. Of course, I briefly summarized these recommendations for the sake of time, but the final guidance contains more granularity on each of these.

If a genetic database meets the recommendations laid out in the final guidance and would like to be recognized by the FDA, there is a voluntary pathway for them to seek recognition. And again, I will just emphasize that this pathway is voluntary.

If so, recognition would occur in three steps. First, a database would voluntarily submit an application to the FDA for recognition. Again, this is a voluntary process and at the discretion of a database administrator, and the FDA is not compelling any database to seek recognition. Second, the FDA would assess the genetic variant database to ensure that all recommendations from the guidance have been met, if applicable.

This would include FDA evaluation of the types of documentation listed here. FDA may also -- as part of the recognition process -- spot check variant assertions to ensure that they are made in accordance with the database's SOPs and reflect the current state of scientific knowledge.

Now finally, once a database has been FDA-recognized, the third step is maintenance of database recognition. The database guidance lays out a process for maintenance of recognition of a database through periodic reassessment of the database, its SOPs, and its assertions.

FDA believes that if a database is recognized, the evidence contained within it could generally constitute valid scientific evidence and could be used to support the clinical validity of genetic and genomic based tests.

The assertions that a database could make about genetic variants could include a variety of statements such as relating to the pathogenicity of a variant. Or whether a somatic variant may be clinically significant.

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 now or in the future. Therefore, we have clarified that it would also be permissible to report these types of assertions too.

Finally, I want to take just the next couple of minutes outlining -- at a high level -- how administrators of databases who are interested in seeking recognition should go about contacting the FDA. We recommend that as a first step, before even submitting and application -- a database administrator should reach out to a member of the Personalized Medicine Staff -- such as myself -- to discuss their pending application.

We can provide advice to the database administrators to help ensure it's a smooth process. Additionally, we can help database administrators target their application to the appropriate review division within FDA. Second, databases - database administrators should compile information demonstrating that they have met all of the recommendations laid out in the guidance -- as they are applicable -- and submit that to the agency using the informational Q Sub process. Excuse me, just to correct. The informational meeting Q Sub process.

Detailed information about the submission process -- including how to format and submit a Q sub -- can be found on our website. And -- as always -- by reaching out to a member of the Personalized Medicine Staff.

So, after FDA receives an application for recognition, FDA staff will review and make a determination about whether or not to grant a database recognition. One question that we get a lot about the recognition process is whether there are any user fees for database recognition. The answer is no. The FDA does not plan to assess user fees for database recognition requests at this time.

You may also ask, well then what are the timelines that FDA will use for reviewing recognition requests? We aim to review database recognition requests within the same timeframe as feedback is typically given during the informational Q Sub submissions. Or -- for those of you who aren't familiar with that -- 90 days.

Finally, if recognition is granted, FDA will alert the database administrator and post this information on our website at the link noted at the bottom of this slide. And there we will also post a summary of our recognition decision.

So now I want to take just a minute to shift into a summary of our key takeaways, and then we'll turn it over for question and answer. So, taken together, these guidance documents discuss the possible future down classification and exemption from pre-market review of NGS-based tests that demonstrate conformity with the standards outlined in this guidance, and that use assertions from FDA-recognized databases.

We believe that this approach offers speed, scalability, and safety.

So, speed. This approach provides test developers with an efficient path to market and connects patients with the current state of clinical knowledge regarding genetic assertions.

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

And finally, safety. This approach encourage innovation while still assuring patients and health care providers that NGS-based tests provide accurate and meaningful results. And now that these guidances are final we look forward to working with the community to implement them and realize their full vision.

To do that we encourage the development of standards that can be used to support the regulatory framework for these tests and the submission of genomic databases for recognition to use to support regulatory decision making. And with that I'll turn it back over to Irene.

Irene Aihie: Operator, we'll now take questions.

Coordinator: Thank you. At this time if you'd like to ask a question please press star one and please record your name when prompted. If you'd like to withdraw the question you may press star two. Again, to ask a question please press star one. One moment please while we wait for the first question.

Dr. Adam Berger: And while we're waiting for those questions, maybe we can go ahead and pose a question ourselves. And, you know, I'll direct one over to Laura.

You mentioned about the database guidance being specific to public databases. Could you comment on whether proprietary databases are eligible for recognition?

Dr. Laura Koontz: So, proprietary databases -- or ones that charge fee for access -- are out of scope of the guidance and would not be eligible for recognition through this guidance. However, these databases -- as I mentioned -- may be sources of valid scientific evidence and could be used to support the clinical validity of a test.

So, individual test developers that rely upon proprietary databases to support their IVDs may need to include supporting information regarding this database in their individual pre-market submissions. And to that end, they might find that the recommendations in this guidance are useful in preparing those pre-market submissions.

Dr. Adam Berger: Great. While we're still waiting for folks to come on with questions maybe we'll just continue an open discussion amongst ourselves a little bit. You know, one thing we've heard from various feedback is that the scope for the guidance on considerations for design, development, and analytical validation of NGS has changed.

And you know, we thought we would go ahead and maybe comment on that a little bit. I'll go ahead and start and maybe then turn it over to Zivana. But you know, I think FDA does not view that the scope of the final guidance has actually changed from the draft.

Both versions actually provide recommendations for designing, developing, and validating NGS-based tests intended to aid clinicians in the diagnosis of symptomatic individuals with suspected germline diseases. However, we did rearrange the scope section a bit in response to some of the comments asking for clarification of what had been perceived as potentially vague language in the draft.

The bulleted list of what is and is not in scope should actually help stakeholders in understanding which tests fall within the scope of the guidance. While the scope is focused, we've noted that the principles may be applicable in some circumstances to tests for some of the uses listed as out of scope and we are actually very happy to have these conversations with individual sponsors. A major reason why these are out of scope is that these tests may have other performance characteristics and/or risk considerations that are not addressed by the recommendations presented in the final guidance.

Dr. Zivana Tezak: Also, we want to add -- because we had heard some feedback that the scope is relatively narrow -- so we want to emphasize that we are well aware that the clinical demand for broader applications of NGS-based diagnostics is increasing.

And we have actually started working with some standards-developing organizations on expanding the potential applicability of the concept - of what the concepts are in the current guidance to maybe have a larger scope. And to that end, CLSI -- or Clinical Laboratory Standards Institute -- has taken on the revision of their sequencing guideline, which is called MM09. And that is about to start in about a month. And from what I understand it's not going to include only germline applications, but probably also somatic and maybe some additional applications. So, we are looking forward to working with the community and seeing what the community and standards organizations can come up with for the scopes that are beyond the current guidance.

But we think that what's laid out in the guidance can be a really good foundation for people to see what we are thinking. And maybe start from there and layer on to that.

Irene Aihie: Okay, we'll go ahead and take our first question.

Coordinator: Thank you. Our first question comes from Lauren Davis. Your line is open.

(Lauren Davis): Oh hi. Yes, Lauren Davis here. And Russell Garlick. The question is probably for Zivana). We have shown -- and others have shown -- that in cancer-associated genes like MSH2, PMS2, BRCA1, BRCA2, there are regions where the insertions and deletions are very hard to detect.

So, my question is, do manufacturers have to demonstrate they can detect these hard-to-detect insertions and deletions in these pathogenic variant types prior to launching their assay?

Dr. Zivana Tezak: So, I think that - and I've - I think I may sound like a broken record. But it will depend on the purpose of the test and on the indications for use, as I think you know.

So, if they are - if the test manufacturer is - manufacturer is claiming that they're detecting certain insertions -- or certain huge either rearrangements in certain genes -- then yes, they should detect - they should have a way to figure out how to prove that they can actually detect those.

Now that goes back to what I was talking about if you have the way to analytically detect certain insertions of certain sizes. But then there are some clinically important ones and that's what I think you are - where you are going with your question.

Which -- for some diseases -- there are some rearrangements or insertions or whatever it is that needs to be detected for that disease. So, you have CFΔ508. You want to detect that. You want to know that you're detecting

that. No matter whether you can detect similar deletions in different parts of the genes.

So, I think the answer to your question is yes. And I think that the follow up answer to that is if we cannot find the clinical samples then samples that are - the reference samples will be probably a good approximation for some of those.

Lauren Davis: Thank you.

Dr. Zivana Tezak: Thank you for the question.

Coordinator: Thank you. And our next question comes from Vera Diaz.

Vera Diaz: Yes, hi. My question's simple. And it's just, on Page Four of the guidance -- Consideration for Design and Development -- is there another document that further expresses what these types of tests might be? So specifically I don't know what type - standalone diagnostic purposes. What type of test would that be?

Dr. Zivana Tezak: So, this guidance is just for aid in diagnosis. Not for standalone. So, you're talking about scope. I can't log into my computer right now to look at what's on Page Four, but I'm thinking you are talking about the scope and what's in and out of the scope?

Vera Diaz: Correct.

Dr. Zivana Tezak: Right. So, this is the only guidance that we right now have for NGS tests.

Vera Diaz: Okay...

Dr. Zivana Tezak: Like I said though, we can build on that. Or community can build on that. And propose and maybe work on some standards for different indications.

Dr. Adam Berger: Hey Zivana, let me just follow up real quick on that as well and just ask you an additional question on that. You know, we've had a lot of discussion around standards and their development.

I was wondering if you might kind of give -- for those that may not be as familiar with it -- our, you know, how we actually recognize standards and the process that standards development organizations actually go through to develop those.

Dr. Zivana Tezak: So, the CDRH at FDA actually has established standards program. And that has been established under FDAMA back in 97. And this program is responsible for facilitating the recognition of both national and international consensus standards.

And then we can use those standards in regulatory review. So - but we can only recognize standards and guidelines that are created by these certified SDOs, or Standard Development Organizations. So, we can't really use the guidelines from professional organizations, even if they might be really, really great.

So, we need standards from SDOs to recognize. And then we can publish in federal register what standards are recognized. And they would be added to the list of recognized consensus standards which can be then found online and you can do the search of FDA-recognized standards and that should pull up the database -- this database of the recognition -- as the first hit.

And there is also -- since the 21st Century Cures -- any interested party may submit a request for recognition of their standard that is established by a nationally or internationally-recognized standard organization. So, in cases of NGS probably it would be something like CLSI or ISO.

Dr. Adam Berger: Okay. Thank you.

Irene Aihie: We'll take our next question.

Coordinator: Thank you. Our next question comes from Ryan Woodhouse. Your line is open.

Ryan Woodhouse: Hello. So, one question I have is that this is targeted towards germline diseases. And so, I was wondering if you would be releasing something similar for tests targeting somatic mutations?

Dr. Zivana Tezak: So yes. So right now, we kind of figured we would start relatively narrow. Because we are -- as you probably noticed -- we are talking not just about the review but we are also talking about down classification and also eventually exemption.

So, we wanted to make sure that we have very narrow intended use. That we can eventually do all that with. Now for somatic, you may be familiar with the recent approvals and even de novo authorizations of several somatic NGS tests that we had. So, we don't anticipate issuing the guidance.

But what you can do is look at the device summaries or summaries of safety and effectiveness of those tests to get some idea of what we are thinking there. And I want to hand it over to Laura to give a little bit more details on that.

Dr. Laura Koontz: Sure. Thanks, Zivana. So, I will mention -- before jumping into the specifics -- that on our website -- on the In-Vitro Diagnostics portion of the CDRH website -- we do have a one-pager that outlines our approach for how we think about the analytical and clinical validation of somatic gene panels or oncopanels.

So, some of the concepts that we have put forward in that white paper -- or not white paper, excuse me, one-pager -- are concepts that, you know, are in line with some of the things in the analytical guidance that Adam and Zivana discussed.

So, for example, for claims outside of companion diagnostic claims. So, for example, Foundation Medicine has 15 different companion diagnostic biomarkers in their test but report back information on 324 different genes as well as two different gene signatures. And MSK -- in their oncopanel, which was authorized last year -- report back information on 468 genes.

For those biomarkers that are not companion diagnostics in both of those authorizations they were able to - the companies were able to leverage a representative approach to validate those biomarkers. So, that's a concept that's really in-line with what we've proposed in the - or what we've put in the final analytical guidance.

And so again -- as Zivana mentioned -- I'd encourage you to take a look at the publicly available decision summaries for both of those documents, which have quite a bit of information about the specific analytical and clinical validation that both - that companies have been doing for somatic oncopanels to date.

And of course, if you have trouble finding that on our website feel free to reach out to us. We can always point you in the right direction.

Ryan Woodhouse: Thank you.

Irene Aihie: Operator, do we have any more questions?

Coordinator: We have no further questions. And again -- as a reminder -- if you'd like to ask a question, please press star one and please record your name when prompted.

Dr. Adam Berger: Well, I'll go ahead and ask one more while we're waiting for others to, you know, join in on the line. I've been - this is for either of you actually. Are test developers required to follow these guidances?

Dr. Zivana Tezak: So, I'll reiterate what Laura said several times. It's that no, these guidances offer one voluntary pathway to the develop and validate NGS-based tests for those who choose to use this pathway.

But -- as usual -- test developers are always free to demonstrate analytical and clinical validity by other means. And they can all always come to us and - in different ways -- like the pre-submissions -- and discuss what those other means they would like to use.

Dr. Adam Berger: It looks like we have one in queue for a question. If we can go ahead and take that.

Coordinator: Thank you. Our next question comes from Marlee Gallant. Your line is open.

Marlee Gallantt: Hi. I just wanted to get back to what you were talking about a moment ago with the test developers that had already gone through the process and used a representative approach to obtain their indications.

And if -- for example -- a test developer has a companion diagnostic indication for a set number of genes, what would the process be for them to have additional genes added to that indication? Would they need to explicitly expand their labeling and could they continue to use that representative process?

Dr. Laura Koontz: So -- oh sorry, that's a loud mic -- so that's a great question. It depends on what types of claims you want to make about those additional variants that you're adding.

If you do want to make a companion diagnostic claim about them then you would need to undergo variant-specific or signature-specific -- whatever the biomarker is -- specific analytical and clinical validation. Like you would for any, you know, first of a kind or follow on companion diagnostic.

For adding additional variants to your panel -- if they are just sort of in this - if they're not those companion diagnostic biomarkers -- you would need to - it would depend on whether or not you had analytically validated them in the original submission whether or not you're able to add them. Or set reporting out on them without an additional submission to the FDA.

So again, I would encourage folks to take a look at that one-pager on our website as well as contact us with any specific questions. Because it's a little bit out of scope for today's webinar, but I think that one-pager has quite a bit of information about in which cases an additional submission would be required or when you can leverage a representative approach.

Marlee Gallant: Thank you.

Coordinator: Thank you. And at this time I show no further questions.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions.

Today's presentation and transcript will be made available on the CDRH Learn web page at www.gov/training/cdrhlearn by Tuesday, June 5. If you have additional questions about today's presentation, please use the contact information provided at the end of the slide presentation.

As always we appreciate your feedback. Following the conclusion of the webinar, please complete a short 13-question survey about your FDA CDRH webinar experience. The survey can be found at www.fda.gov/cdrhwebinar immediately following the conclusion of today's live webinar.

Again, thank you for participating. This concludes today's webinar.

Coordinator: Thank you. This concludes today's conference. You may disconnect at this time. Thank you.

END