FDA Webinar: Next Generation Sequencing (NGS) Draft Guidances: Implications for Patients and Providers

Moderator: Irene Aihie
July 27, 2016
1:30 pm ET

Coordinator: Good afternoon and thank you all for holding. Your lines have been placed on a listen-only mode until the question and answer portion of today's conference. And I'd like to remind all parties the call is now being recorded, if you have any objections to please disconnect at this time. And I would now like to turn the call over to 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 and Education. As a point of information please check your inbox for an email from the FDA with updated login information for today's call. On July 6, 2016 the US Food and Drug Administration issued two draft guide thesis that when finalized will provide a flexible and streamlined approach to FDA's oversight of next-generation sequencing. These two drug guidances support President Obama's Precision Medicine Initiative, PMI which aims to take advantage of the progress made in genomic testing to accelerate the development of new treatments that take into account individual differences in people's genes, environment and lifestyles.

The purpose of today's Webinar is to address the significance of these guidance for patients and healthcare professionals. Your presenters today are Dr. David Litwack and Dr. Laura Koontz both from the Personalized Medicine Staff here in CDRH. Following the presentation we will open the lines for your questions related to the technical regulatory aspect of the guidance. Additionally, other center subject matter experts will be joining in the Q&A portion of our Webinar. Now I give you David.

Dr. David Litwack: Thank you Irene and thank you very much to all the people who called in to join us for the second of two Webinars on the two next-generation sequencing draft guidances we released on July 6. Unlike the previous hour which really focused more on the technical aspects and regulatory details of the guidances we'd like to take this hour to discuss what these guidances may mean for patients and providers.

So what we would like to do in this hour is to provide some context and an overview of the guidances with really - and really to focus more on what - to focus on what these may mean for patients and providers and some of the features that we have included with patients and providers in mind, for both the analytical guidance, the guidance on the analytical standards for NGS, and for the database guidance. We want to discuss how we think these guidances will advance personalized medicine and improve patient care and answer your questions about the past guidances and also provide some background so you submit comments to FDA. These are draft guidance's and we really encourage you to provide your input and suggestions.

All right so we're going to start by just briefly discussing FDA's role in the Precision Medicine Initiative which just sort of motivated these two guidances and then review the two guidances. I'll discuss the analytical standards guidance and then Dr. Koontz will take over and discuss the genetic database

draft guidance. She'll discuss the next steps and then we'll take care of questions.

So first a little background. So the White House Precision Medicine Initiative was announced by President Obama in the state of the Union address in January 2015. And the goal of this is to enable a new era of medicine through research technology and policies that empower patients, researchers and providers to work together toward development of individualized care. You're probably all familiar with the - if you've been following the PMI - with the Million Person cohort, but the PMI also recognizes that one of the essential needs of precision medicine is the availability of accurate and reliable diagnostic tests because the results from these tests provide the basis for future research and also are needed for care, and to help patients, guide patients and providers in making medical decisions.

So excuse me, we're having a little technical issue. Hold on just…

Irene Aihie: There you go.

Dr. David Litwack: …(unintelligible) Thank you. Okay so the - right, so FDA's role in the PMI, our proposal was really to optimize our regulatory oversight of next generation sequencing tests. We recognize that these tests are very important to patients and providers. They're innovative. They provide new - they provide new information and diagnostic results that patients need. But at the same time we recognize that patients and providers want to be assured that the test results they get are accurate - that they're accurate. So we want to help ensure the accuracy of genetic tests.

We also understand that patients and providers want innovative new tests but at the same time they may be struggling -- and we've heard this from a

number of sources - that the information they're getting from genetic tests - they are struggling with understanding what those test results mean and how they should guide clinical care and clinical decision-making.

So in our proposal in optimizing our regulatory oversight of next-generation sequencing tests we want to develop an oversight approach that's well-suited to the unique nature of NGS tests, that is taking advantage of the rapid evolution of this technology and the rapid changes of evidence, in evidence, for variants that are detected by NGS tests. And, - as part of that approach - we want a more dynamic system that will allow that rapid progress and hence innovation while still ensuring that the tests that are used are safe and effective.

So these two draft guidances are really our first steps to getting this more dynamic regulatory system that I was just discussing. They are designed to anticipate and support the needs of rapidly evolving NGS technologies. They also are designed to support reliable, accurate, and understandable test results. So this is one of the outcomes that we would really like for our patients and their providers, which is to improve understanding and confidence in these tests, confidence in the results that they're getting.

We also want to promote an efficient path to market for all tests - all developers of NGS tests - and we want to do it by encouraging the development and the use of standards to ensure test quality. We want to recognize third-party genetic databases for evidence on the clinical relevance that will dynamically present new observations and in many cases expert evaluation of evidence.

Currently, with the first draft guidance we are describing a regulatory pathway for NGS based tests for certain uses but we do plan to expand to more global

applications - more uses of NGS based tests. And this is - I want to stress that this whole approach is based in many ways on having open processes and accessibility, so in other words, transparency, that everybody who uses these tests should know what their performance is and what the available evidence supporting their test results are.

This is important obviously for patient care at the current time but I also want to make the point that, as part of a system of precision medicine, having these tests work properly and having the evidence evaluated in a way that we can rely on is critical for future research and the advance of precision medicine because the data that we get from the clinical use of NGS is going to be used as the base of research for future development in this field - for future diagnostic tests and for future therapies and cures. So we all have an interest in assuring that this source of data is sound so that we can get the most out of our future research.

In designing any regulatory – any,, new approach to regulatory oversight it's been very important for us to make sure that the core assurances provided by FDA premarket review are not lost and we've tried to embody that in these guidance's. There are three elements I want to point out here that we particularly paid attention to. One is analytical validity. In other words does the test detect in this case - for NGS = does it detect the variant that you have and does it not detect the variant that you don't have? So you don't want to hear - you don't want to find out you have a variant that you don't actually have and you don't want to miss a variant that you do have because that may affect in some cases your clinical decision-making. So making sure test results are accurate and correct and reliable is very important.

We also look at clinical validity and this just means, if you're detecting a variant - is a variant correctly identifying your disease or condition or is it

correctly directing you to appropriate care? We – this is where evidence, clinical evidence and expert evaluation is the key. And we all have an interest in making sure that whatever evidence exists for NGS - we want that to be transparent and we want everybody to understand it and understand how it was evaluated.

And finally the labeling. So what is said about the test by the person, the test developer? Are the directions clear for test developers? Is what you say about the test truthful and not misleading?

One of our concerns at FDA is of course that people don't make false claims about tests. And we want to make sure that that is also incorporated into any new approach that we have. And this is all of course based on what the intended use of a test is. So, if the test is used for hereditary genetics it's going to be different than diagnosing, maybe somebody with some - with hearing loss or something. It's going to be different and some of these aspects may be different than a test that is designed to detect somatic mutations in a tumor.

So let me move on to the two guidances. Before we start with the analytical we'll start with the analytical standards guidance. And this one is entitled as you can see The Use of Standards and FDA Regulatory Oversight of NGS Based IVDs Used for Diagnosing Germline Diseases. So in the next slide just to motivate this a little bit one of the differences and one of the reasons for proposing a new approach is - we recognize NGS based tests have some unique features that we're trying to accommodate and this was one of them - that unlike most conventional diagnostics which analyze one or a few or at least a predefined number of analytes, NGS based diagnostics can basically have - can detect any number of - any undefined number of variants. You can't predict ahead of time what you're going to find.

So, you know, if you think about a glucose test it's designed to detect glucose but with 3 billion variants - 3 billion bases in the human genome we have almost an infinite space here. And so our tradition, our conventional approach of looking at analytical performance for each particular analyte in a premarket submission we feel is not really possible with NGS based diagnostics. So we've looked to a more process-based and standards-based approach to provide the assurance that these tests perform well and provide accurate results. So let me talk a little bit about what that means. So the next slide.

Actually before I get to that let me point out and you may have noticed that, you know, depending on where your - you may have noticed that the title of this specifies only germline disorders. So as I said, this guidance is the first step in - these two guidances are first steps in developing this new approach. We decided for a variety of reasons that it was best to start with sequencing of germline DNA for - of DNA to detect germline variancets to act as an aid in diagnosis for hereditary disorders. There are obviously a number of cases of NGS that fall outside that scope including for oncology purposes.

And the - we do want to expand this approach to all those uses. It's a very high priority for us. But for a number of reasons we thought it best to focus on what we consider to be a lower risk and a generally technically simpler case which is hereditary disorders. Within this bin we propose these broad intended uses so any number of indications could fall within that.

So what is in the analytical standards guidance? Well mostly this is aimed at people, at test developers or sponsors. It includes recommendations, technical recommendation for how one ought to design a test and the way in which one might assure that the test performs in a way that will meet the needs of the user and the intended or indications for use of the test. So it really is about recommendations that could act as standards for a process for test design. It

doesn't really focus on saying all tests should include this particular component or meet this particular level of performance because we recognize there's a wide variety of ways in which tests even for the same intended use may be designed and used and we want to accommodate that, as we feel that's the way we will continue to get innovation in this field.

One particular thing I do want to point out here are test reports - that we do provide recommendations for test reporting. And one of our goals based on input we've received in a number of forums, including a March 2 workshopspecifically designed to get the input of patients and providers, is the confusion that is caused by the lack of standardized test reports and the lack of clear language describing what the clinical meaning of variants are.

And so one of the things we discussed in this guidance is and we would like to promote by this approach is the ability to standardize tests and to provide clear language. And so on this point we really encourage all of you to provide comment and input on this because we believe this will be - this is something we believe we can promote going forward.

So the overall - the other thing this guidance describes is a path to market which I won't go into - a regulatory path for these that will allow us to implement these recommendations potentially as standards and will lower the bar for test developers, and that is something I won't go into any more detail here but we discussed in the last hour. The benefits of this approach is to make it easier for test developers to develop and market their tests while at the same time accommodating differences in use. And we believe that the recommendations we put forward can form the basis of a standard that could be clear and that all test developers could - that we do all of these things while providing the assurances of accuracy.

So the final point I'd like to make is in addition to test reporting we also have recommendations around transparency - that we believe if we move to a standards based approach providing transparency on test performance is critical for users of these tests so they understand what they're getting. So at this point I'll end and will hand it over to Dr. Koontz who will discuss the genetic database draft guidance.

Dr. Laura Koontz: Thanks David. So my name is Laura Koontz and I'm a member of the Personalized Medicine Staff here at FDA. And I'll now take the next couple of minutes to discuss the second of our draft guidance documents, the use of public genetic variant databases to support clinical validity for next-generation sequencing based in vitro diagnostics. This guidance outlines the agency's thinking about how genetic databases that follow certain quality recommendations can be used to support the regulatory review of NGS based tests.

So NGS based tests pose interesting - whoops, I forgot to advance a slide, sorry. So these tests pose interesting challenges to both FDA reviewers and test developers. As David mentioned conventional diagnostics typically only measure a couple of analytes, maybe even just one. For example blood glucose tests measure blood glucose. And so it's relatively straightforward for a test developer to think about how to undertake the clinical studies necessary to link blood glucose to a disease or condition, in this example diabetes. And sometimes a sponsor of a diagnostic test will initiate these studies on their own.

On the other hand NGS based diagnostics have the ability to test and detect a large number, maybe even millions of analytes, in this case analytes being genetic variations. So depending upon the type of tests being run some of these genetic variants may be rare, potentially only occurring in a couple of

people in the world. And it's clearly impractical and burdensome for a single test developer to generate all of the evidence necessary to link a potentially actionable genetic variant to a disease especially for the case of rare variants.

So imagine if you were a test developer in the United States with an idea for a test where you needed to find patients with a particular genetic mutation or a family of mutations to enroll in your clinical study or imagine that you're a patient with a rare genetic variant looking to find out information about other patients like you. Genetic databases allow information from people all over the world to be compiled in one place. A test developer may be able to find enough information about the association between a genetic variant they are interested in designing a test for and a disease or condition if they look in genetic databases.

This could expand the evidence base supporting the clinical validity of a test dramatically. Crowdsourcing evidence in this manner could mean that better tests get to the market faster and benefit patients sooner. But of course these databases can be incredibly useful to patients seeking to learn more information about their own disease or condition, but we won't really be discussing that anymore today. Again of course this is a simplified example but it illustrates the point about the power, the potential power of these databases.

So how does the ability to tap into a publicly available database to support clinical claims made by a test actually benefit patients? Databases of genetic variants have the potential to speed evidence development for NGS based tests since the evidence housed in these database is typically generated by multiple parties. Collectively we can obtain evidence for the clinical interpretation of a greater portion of the genome then we can individually.

Again crowdsourcing evidence in this way eases the burden on any single test developer and could speed new tests to the marketplace.

And importantly aggregated data could also provide a stronger evidence base for NGS based tests. That is, tests that use these databases would be connected with the current state of scientific knowledge regarding a genetic variant and its relationship to a disease or a condition. Finally, FDA believes that as more evidence is gathered and incorporated into these databases new assertions supported by that evidence could likely be made by a database. To allow NGS based test developers to leverage these databases FDA published this draft guidance which lays out how genetic variant databases can be sources of valid scientific evidence to support their regulatory review of NGS based test.

I'll just point out valid scientific evidence is a regulatory term and that is the basis of regulatory review for diagnostics. So specifically the database guidance lays out a series of recommendations that FDA believes when followed would assure the quality of the data within a database and therefore allow the database to be considered a source of valid scientific evidence which could then be used to support the clinical validity of an NGS based test. Database administrators that run databases that meet these recommendations could voluntarily apply for FDA recognition. Again it's voluntary.

They would submit an application to FDA demonstrating that their database met all of those recommendations set forth in the guidance. And these recommendations broadly rest upon three pillars. So number one is transparency. Is the database publicly accessible? Are there adequate data provenance included with the variants? Is there versioning information? Are there SOPs used for curation and interpretation publicly available?

The second is the use of validated processes and formal procedures. So are there formal procedures in place for database operations? Are the variant assertions made using a validated decision matrix?

And then the third pillar is expert interpretation. So are the people doing the curation and interpretation experts? And are there mechanisms in place to check assertions that are being made and ensure that they're being done according to the defined processes that the database itself has laid out?

So we believe that if these recommendations and again several others detailed in the guidance -- for the sake of time we're not going through all of them here today -- are met then the database could apply for and potentially be granted FDA recognition. Test developers could then use these FDA recognized databases to support the regulatory review of their tests.

So to become an FDA recognized database the database initiator would have to demonstrate that those recommendations were met. And this recognition would occur in three steps. So first a database voluntarily submits an application to the FDA for recognition. And again I just want to emphasize that this process is voluntary and at the discretion of the database administrator. FDA is not compelling any database to seek recognition.

Second the FDA would assess the genetic variant database policies and procedures to ensure that they meet these recommendations. And that's, again, included in the information that would be submitted as part of an application. FDA would also spotcheck the variant assertions made by the database to ensure that they are following their - the database's SOPs for variant curation and interpretation. Third and finally once a database is recognized, the guidance lays out a process for maintenance of FDA recognition of the

database through periodic reassessment of the database, its SOPs and assertions.

So FDA believes that the evidence contained in FDA recognized databases which conform to the outline recommendation would generally constitute valid scientific evidence and again could be used to demonstrate the clinical validity of a test. The assertions that a database could make about a genetic variant include a variant types such as relating to the pathogenicity of a variant or whether a variant is likely to confer a response or nonresponse to a class of medication or a certain therapy.

Importantly at our public workshop in March of this past year of this year we've heard that it was also important for patients and providers to receive information regarding the variants of uncertain significance as this may be medical useful information for an individual patient. Therefore we have proposed that it would be permissible to report these types of variance assertions but again FDA would like to receive input on this point.

All variant assertions should be supported by adequate information detailing the evidence within the database supporting that assertion regardless of what type it is whether it's a pathogenic variant assertion or a VUS. For example, we would like to have information regarding how many times a variant has been seen in people with a certain disease or condition, what is the biochemical data that links that gene to a disease? What type of variant is it and what does that confer to the protein that it encodes 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. We believe that these recommendations dovetail with those regarding test reports in the analytical standards guidance that David mentioned. Those

recommendations state, among other things, that the relationship between a reported variant and a clinical disease or condition must be clearly stated on a test report.

And so in summary this guidance document outlines an approach that allows the test developers to take advantage of the benefits of data aggregated in an FDA recognized database to support the regulatory review of their test and outlines a pathway for databases to voluntarily seek recognition. Again we believe that this - the database guidance would enable patients and providers to receive results about a variety of genetic variance provided they're supported by adequate evidence within a database. FDAs further believes that by encouraging crowdsourcing of evidence generation and hopefully spurring data sharing that this approach could advance precision medicine.

The database guidance in combination with the analytical standards guidance discuss the possible future down classification and exemption from premarket review of NGS based tests that demonstrate conformity with the standards outlined in the analyticals standard guidance and use assertions from FDA recognized databases. FDA believes that this approach offers speed, scalability and safety. So taking speed, this approach when finalized would provide test developers with an efficient path to market and connect patients with tests more quickly. Scalability: test developers both large and small could benefit from this approach because it's based on standards and evidence that everyone can access. And safety: this approach encourages innovation while still ensuring patients and healthcare providers that the tests that they rely upon to make clinical decisions are safe and effective and that they provide accurate and meaningful results to patients.

Okay. I'd like to just briefly go through the next steps before we move on to the Q&A. So currently the draft guidance documents are open for public

comment with the docket scheduled to close on October 6. During the public comment period we also plan to hold a public workshop later this fall to discuss the guidances. And we hope to be able to announce that soon so please keep your eyes open for that announcement.

Following the closure of the open comment period we'll analyze the comments, make necessarily changes based on public feedback and move towards finalization and implementation. And eventually we hope to be able to expand this approach to other intended uses of NGS based tests such as the ones that David showed earlier like oncology for example. And we'll have the opportunity for the community to comment on additional standards or criteria that would be necessary to ensure the safety and effectiveness of these types of tests.

So as I mentioned that comment period closes on October 6 and we hope that you'll submit comments regarding the substance of each of these guidances, what you think we got right, what we didn't, what we need to change. And I just also want to take this moment to point out that each of these guidances is accompanied by a Federal Register notice which includes a section of questions that the agency has and is seeking additional feedback from the committee on.

So as you're developing your comments I encourage you to look at these questions for your consideration and offer your feedback on them to us. With that, I'm happy to turn it back over to Irene.

Irene Aihie: We'll now take questions.

Coordinator: Thank you. And on the audio portion if you would like to ask a question please press Star 1, please unmute your phone and record your name clearly

when prompted. Once again if you'd like to ask a question please press Star 1 and one moment please. Our first question today is from (Eric Koenig).

(Eric Konnick): Hi. I'd like a little bit of clarification on the issue of FDA validated or cleared databases. So routinely are you stated multiple times that this is to support the clinical validity of different tests. However in both Webinars as well as some other comments that have been made you stated things such as you would allow the USes to be - were okay to report. And so that kind of brings up the issue of if a individual laboratory disagrees within assertion made in one of these databases or they find a variance that isn't in the database and they want to report that to the patient and the provider what is the FDA's take on that? Are these databases for clinical reporting? Are they for clinical validity or are they for both?

Elizabeth Mansfield: So the purpose of the database in the draft guidance on the databases was our sense was to say that to provide valid scientific evidence that could support a claim of clinical validity. We realize that laboratories often will see different variants and news variants that they've never seen before. We believe in that case you would be doing your own expert interpretation and that you would report that out essentially as whatever your interpretation was.

If you wanted to claim later on the cheer test detected that various and that it had particular pathogenicity or if it was benign or (DUF). And then the approach that we're proposing would we hope allow you to do that without necessarily coming back to us to check in whether that claim was okay with us. It would be hopefully something that you would have put into a database, it would now be in the database and you could point to the database and say that it was there. I hope that I (unintelligible).

(Erik Koenig): So let me make sure this is clear then. So as a physician reporting a variance that's not in a database that I am making an assertion of what I think the pathogenicity is based on the data that is available that is allowed under the FDAs take on this practice?

Woman 1: Well we didn't really address this in the guidance because we have not completely addressed the entire regulatory process through these guidances. But one of our goals is to allow the clinical test to keep up with the science. And so in a sense this could be considered a type of off label use. It would be an expert interpretation by the laboratory professional because there's no other information about that particular mutation or variance that you've seen.

(Erik Koenig): So it just it's interesting. You say from off label use because in other areas of medical practice it's just the practice of medicine where we're making an assessment of the evidence and then making a determination based on our expert opinion so that's…

Woman 1: Yes that's often…

(Erik Koenig): …a - that's like…

Woman 1: what off label use constitutes and medical devices and other therapeutic products where a medical professional uses his or her own judgment to use a test or therapeutic product in a way that differs from the specific labels of the product.

(Erik Koenig): So I definitely recommend that in all of these guidances there's a very clear extension of how the practice of medicine fits into the rubric that you're creating here.

Woman 1: Thanks and please - I think we've talked to you before. Please submit your comments to the docket so that we can be sure that we take those specifically in consideration.

(Erik Koenig): I will add them to my multiple comments. I'll resubmit it.

Woman 1: Thank you.

Coordinator: Thank you. And as a reminder to ask a question please press Star 1. And our next question is from (Jay Q.).

(Jay Q.): Hi. I just want to get your opinion of the NGS phased testing provided by the clear certified labs. You know, some of them are in the market and then they're supplying data to the physicians so what's your comments on that part?

Woman 1: So currently we expect any - sorry for the feedback (unintelligible). Currently we expect that any test for which a result is provided back for medical purposes be offered through a laboratory that's in compliance with the clear regulations. So that's our understanding that we do not administer the clear regulation. So I would defer you to CMS if you had more questions about that.

(Jay Q.): Okay thank you.

Coordinator: Thank you. And as a reminder to ask a question please press Star 1. And our next question is from (Juan Mao).

(Juan Mao): Hi. Hello. I have a question - oh I hear my echo. Do you hear me?

Woman 1: Yes. We can hear you.

(Juan Mao): Okay. So my question may go a little bit beyond the current documentation but it's kind of related. So as the science continues to progress right our understanding of the mutation or variance may change over time. Could you let us hear that for the FDA has any thoughts on guidance about reissuing reports? So like for example that a report was issued by a clear lab to a medical doctor on January 1, 2016 and let's say that a year later some of the variance that was previously included in the report has changed its classifications. So how to do with those scenarios?

(Nan Silvia): This is (Nan Silvia). I'll take this one. So in the case that the interpretation of a variant would change over time the first thing I want to say about that is that our expectation is that a given assertion would be a - would be tied to a version of the database. And we've asked the database to be versioning. But we do expect that if variants change over time that the community who is in the middle of a big discussion about re-contacting patients and telling them that their variant interpretation has changed that the community will have worked out that and decided what the process is. FDA does not specifically - has not specifically formulated any policy around that and we think that it might best be dealt with by the community.

Dr. David Litwack: And let me just add that I think our hope - one of our hopes is with the databases, the databases that eventually we can get to a point where the evidence at any particular time is available to people. So whether or not there was free contacting there would be a place for people to go if they needed to look at what the, you know, if they needed to go back to their genetic test report.

(Juan Mao): Thank you.

Coordinator: Thank you. And as a reminder to ask a question please press Star 1. One moment please. I am showing no further questions at this time. I'd now like to turn the call back to Irene for closing remarks.

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 CDRH Learn Web page 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. And this does conclude today's conference. You may disconnect at this time.

END