DEPARTMENT OF HEALTH AND HUMAN SERVICES

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STATEMENT

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UNITED STATES SENATE

"Continuing America's Leadership: Realizing the Promise of Precision Medicine for Patients"

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Chairman Alexander, Ranking Member Murray, and Members of the Committee, I am Dr. Jeffrey Shuren, Director, Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to be here today to discuss the important role FDA is playing in the Administration's Precision Medicine Initiative as part of our mission to protect and promote the public health by ensuring the safety, efficacy, and quality of medical products.

The President's Precision Medicine Initiative, launched in January 2015, is a new effort to revolutionize how we improve health and treat disease in the United States. The initiative will pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and equip clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients. Additionally, through collaborative public and private efforts, the initiative will leverage advances in genomics, emerging methods for managing and analyzing large data sets, and health information technology to accelerate biomedical discoveries, all while protecting patient privacy.

A key technology that will advance the Precision Medicine Initiative is Next-Generation Sequencing (NGS) technology.[1] NGS tests can rapidly sequence large segments of an individual's DNA and even an individual's entire genome. In fact, an NGS test is capable of detecting the billions of bases in the human genome, and in doing so identify the approximately 3 million genetic variants an individual may have. A single use of an NGS test could enable the

[1] Next-Generation Sequencing, also referred to as "massively parallel sequencing" or "high-throughput sequencing," refers to technologies that perform DNA sequencing in parallel, allowing for the production of thousands or millions of sequences concurrently.

diagnosis of any one, or more, diseases or conditions a patient presents with or help to predict a patient's risk for numerous conditions.

The use of NGS tests also is accelerating the pace of scientific discovery, as the compilation of large amounts of genetic information in scientific databases and electronic health records enables scientists to perform observational studies and computer modeling to better understand whether and how certain genetic variants, including very rare variants, are linked to certain conditions and diseases. As the Initiative moves forward, we expect NGS technologies to play a central role in both research and clinical practice.

For precision medicine to succeed, NGS tests must be accurate, reliable, and clinically meaningful. As with other diagnostic tests, an inaccurate NGS test can lead to patients receiving the wrong diagnosis,[2] the wrong treatment, or no treatment at all, even when effective therapy is available. Inaccurate NGS tests can impose unnecessary costs on the health care system. Inaccurate tests could cause healthy individuals to seek further testing and treatment to address an erroneous belief that they have, or could develop, a certain condition or disease. As an example, if a patient was informed that she had a dominant mutation that confers increased risk for breast and ovarian cancer, that patient might choose to have complete mastectomy and hysterectomy, in order to prevent future cancer. In addition, the patient's family would be alerted to their own genetic risk. If the test results were inaccurate, the prophylactic surgery and all the family follow-up may not have been necessary. As treatment for cancer becomes more influenced by genetic testing of the tumor, and treatment

[2] Here, "diagnosis" refers to the "diagnosis of disease and other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease" (21 *Code of Federal Regulations* 809.3(a)), and includes but is not limited to diagnosis, aid in diagnosis, prognosis, therapy selection/dosing, monitoring, and risk prediction.

based on type of mutation, it is increasingly important to ensure accurate and reliable tests. Thus, FDA oversight is critical to protect the public health and to maximize the benefits of precision medicine.

The capabilities of NGS tests and their rapid evolution, however, pose unique challenges to applying FDA's traditional regulatory approach for determining whether a diagnostic test is accurate and reliable (analytical performance) and if the results from the test correctly identify the relevant disease or condition (clinical performance) on a test-by-test basis. Specific challenges related to NGS tests include:

- The need to evaluate the ability of the test to produce accurate and reliable results. Because NGS can identify an essentially unlimited number of variants, it would be difficult, if not impossible, to demonstrate performance on every possible detectable variant, as it would for other tests. Instead, FDA has accepted novel strategies to demonstrate the analytical performance of NGS tests while maintaining appropriate oversight to protect patients.
- Because NGS tests can routinely identify variants that are shared by only a few individuals, traditional clinical studies establishing the link of such variants to disease are not feasible. Instead, the clinical performance of NGS tests will rest in many cases on the ability to aggregate evidence from many diverse sources.

Although the unique features of NGS tests create regulatory challenges, these same features also provide opportunities for novel solutions to regulatory oversight:

- The accumulation of data from NGS testing is enabling scientists, clinical labs, and regulators to better understand NGS outputs and error modes. NGS used in research and in diagnostic testing is generating a large amount of data that can be leveraged in further research, clinical trials, databases, and learning health systems to further evaluate the analytical and clinical performance of NGS tests.
- The large amount of cross-genome data generated by NGS tests could allow unique approaches, such as novel metrics and computational approaches, for assessing test performance.
- More generally, the cumulative generation of data through the increased use of NGS testing could help spur additional research in genomics and precision medicine.

The challenges and opportunities described above are now presenting themselves as realities because of the critical mass of genomic data that has been accumulated by researchers and clinicians. Thus, it is clear that new regulatory approaches will be needed to enable the Agency to provide appropriate oversight, in a way that is more suitable to the complexity and data-richness of this new technology, and to ensure that NGS tests have adequate analytical and clinical performance.

Recognizing the importance of NGS tests under the President's Precision Medicine Initiative, FDA is committed to developing a new approach for evaluating NGS tests. The work under the President's Precision Medicine Initiative builds off of efforts FDA has taken in the last several years to understand NGS technologies and to identify a regulatory framework that ensures safety and effectiveness while enabling innovation in the field.

Since 2011, FDA has hosted several public workshops examining various aspects of NGS, and has interacted extensively with scientists and other subject matter experts at conferences and in other professional venues. In addition, FDA personnel have also participated in developing standards and tools for the scientific community, such as the Next-Generation Sequencing: Standardization of Clinical Testing (Nex-StoCT) Workgroup and the Genome in a Bottle Consortium. These efforts helped to inform the essential elements of a new regulatory approach to NGS technologies.

In 2013, FDA cleared the first NGS instrument as well as two NGS tests for cystic fibrosis. In doing so, the Agency adapted its traditional regulatory approach to diagnostics. For instance, FDA was able to rely on a well-curated, shared database in assessing the validity of the 139 genetic variants involved in the assay, rather than requiring the test's manufacturer to independently generate data to support each variant's association with the disease. This not only reduced the burden for the manufacturer, it significantly improved the timeliness with which the product was able to be made available to clinicians and the public.

FDA now seeks to build on its successful past approaches to create an efficient and dynamic system for providing regulatory oversight of NGS tests. In December 2014, the Agency issued a discussion paper, *Optimizing FDA's regulatory oversight of next generation sequencing diagnostic tests – preliminary discussion paper*, [3] to gain public feedback. The paper outlines new regulatory approaches under consideration for both analytical and clinical performance of NGS tests.

[3] Food and Drug Administration. Optimizing FDA's regulatory oversight of next generation sequencing diagnostic tests – preliminary discussion paper.
http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM427869.pdf

For analytical performance, the paper discusses an approach based on the development of quality-based standards[4] for NGS test performance. These standards would be created in collaboration with the leading experts from the field of genomics. Conformance to such a standard could potentially provide assurance that an NGS test meets an acceptable level of performance, and that the results generated are reliable and accurate.

For clinical performance, the paper discusses the use of high-quality curated genetic databases that provide information on genetic variants and their association with disease to better establish the clinical performance of NGS tests by providing evidence about such associations and the strength of that evidence. As an example, NIH has created the ClinVar database, which houses information about genetic variants and their association with disease that has been shared by clinical laboratories, researchers, and other sources. Recently, NIH has funded external geneticists to curate entries in the ClinVar databases, under a program called ClinGen. FDA is now collaborating with NIH to understand how to use the curated data in ClinVar to support regulatory review of NGS tests. Use of curated databases, such as ClinVar, can provide a dynamic system for test developers to capture and update the clinical meaning of their tests, based on the latest evidence.

Both of these components—a standards-based approach to test performance and the use of community-generated evidence—could provide a dynamic and efficient regulatory system that could enable developers and users to seamlessly alter and improve their NGS tests as needed to advance the practice of precision medicine to benefit patients.

[4] Here, the term "standards" encompasses: metrics and tools that can assess the metrics, best practices, and more specific technical or other standards that would be developed by a recognized body.

A key component of FDA's work under the President's Precision Medicine Initiative is to engage with stakeholders to inform any new regulatory approach adopted for NGS tests. Moreover, FDA is committed to drawing on the knowledge of the scientific community to help inform the Agency's approach to NGS oversight. Thus, the first action taken by FDA, after the launch of the Precision Medicine Initiative, was holding a public meeting in February 2015, with a broad range of stakeholders to discuss the regulatory approaches outlined in FDA's NGS discussion paper, and to hear experiences and ideas on NGS from the clinical and research communities. Nearly 1,000 individuals attended the meeting, and there was general consensus that an innovative regulatory approach was needed in order to balance NGS innovation and appropriate oversight. FDA is now reviewing feedback from the stakeholders to inform the development of more specific regulatory proposals that will be released for public comment.

As a first step to creating these proposals, FDA is meeting with the scientific community and other stakeholders to develop the standards, technical solutions, and best practices necessary to create a comprehensive proposal. In FY2015 and FY2016, FDA plans to issue additional white papers, and, if necessary, guidance, and convene further public workshops to work out the specifics.

To support this essential work, the President's FY2016 budget includes $10 million to FDA to acquire additional expertise and advance the development of the regulatory structure needed to advance innovation in precision medicine and protect public health.

We now are entering a time of rapid scientific advancement with an eye toward precision medicine occurring in everyday clinical practice. For precision medicine to fully succeed, our

regulatory approach must be crafted in a manner that facilitates innovation, is sufficiently nimble to new scientific and technological advances, allows the public to have timely access to newly developed tests, and ensures that those tests are accurate, reliable, and clinically relevant.

Thank you for your continued interest in this important topic and for the opportunity to testify regarding FDA's contributions to progress on this issue. I am happy to answer any questions you may have.