



March 20, 2015

ATTN: Leslie Kux  
Associate Commissioner for Policy  
Food and Drug Administration  
Division of Dockets Management (HFA-305)  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: Docket No. FDA-2014-N-2214

*Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests – Preliminary Discussion Paper*

Submitted electronically via <http://www.regulations.gov>

Dear Associate Commissioner Kux:

The Personalized Medicine Coalition (PMC) appreciates the opportunity to submit comments regarding the U.S. Food and Drug Administration (FDA)'s preliminary discussion paper, *Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests*. The discussion paper raises considerations and poses specific questions related to some novel ways of thinking about potential oversight mechanisms for next generation sequencing (NGS) diagnostic tests.

PMC, representing innovators, scientists, patients, providers, and payers, promotes the understanding and adoption of personalized medicine concepts, services, and products to benefit patients and the health system.

Personalized medicine is an emerging field that uses diagnostic tools to identify specific biological markers, often genetic, that help determine which medical treatments and procedures will work best for each patient. By combining this information with an individual's medical records and circumstances, personalized medicine allows doctors and patients to develop targeted prevention and treatment plans.

Our interest in the discussion paper pertains to how the concepts therein can support this emerging field. NGS technologies hold great promise for advancing personalized medicine. The ability to know one's genomic data can and will change the way that physicians and patients evaluate personal health. NGS will allow for the identification of many of the genetic variants an individual or his or her tumor can have. This information can be used to make health care decisions based on the genetic makeup of each individual patient, thus truly personalizing health care strategies.

While NGS holds great promise for the future of health care, appropriate regulatory oversight of these innovations will be needed to protect patients. Providing optimal access to

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high-quality diagnostic tests will help deliver on the promise of personalized medicine while protecting patients and public health.

### **Scope and Statement of Neutrality**

Many of PMC's members will present their own responses to the agency and will actively advocate for those positions. PMC's comments are designed to provide feedback on the preliminary discussion paper so that the general concept of personalized medicine can advance. These comments are not intended to impact adversely the ability of individual PMC members, alone or in combination, to pursue separate comments with respect to the preliminary discussion paper or related issues. PMC's response is focused exclusively on personalized medicine issues related to all genomic diagnostic tests, including NGS and all accompanying technologies (the combination of these is referred to herein as NGS).

Since our comments are focused on how NGS technologies can advance personalized medicine, and because there are some differences of opinion within our membership, PMC will not take a position on whether FDA has the statutory authority to regulate laboratory developed tests (LDTs) as medical devices or on the processes by which FDA may regulate them.

### **Acknowledgement of FDA's Efforts on NGS**

NGS oversight represents a new frontier in regulatory processes. A single NGS test can identify multiple genetic variants, and the results of the test could lead to useful information about many different health conditions. Traditional methods of oversight for diagnostic tests based on the use of multiple randomized clinical trials for validation of each specific clinical endpoint are impractical for these kinds of dynamic tools. The preliminary discussion paper represents new ways of thinking about regulation of advanced genomic technologies, and we view the consideration of approaches discussed therein as an excellent start.

PMC appreciates that FDA is engaging diverse stakeholders at the earliest stages of development in order to promote thought and incorporate various perspectives. We encourage FDA to continue that engagement, and look forward to working with the agency on this topic.

### **Assumptions in the Preliminary Discussion Paper**

The preliminary discussion paper makes some notable assumptions which the PMC will not dispute by way of these comments, but for which we note that further clarity will need to be established before the concepts described herein can be placed in an appropriate context.

First, the preliminary draft assumes that FDA will regulate laboratory developed NGS tests as medical devices. As noted above, PMC will not take a position on the FDA's statutory authority on this point, but offers these comments in the context of this assumption so as to help promote the advancement of personalized medicine as related to NGS.

Second, the preliminary draft assumes that any processes for oversight of NGS diagnostic tests will be equally applicable to laboratories and IVD manufacturers without the creation of a differentiated pathway for either group. Moving forward, it is important to consider issues such as administrative burden, potential for multiple regulatory requirements (FDA and CLIA), and practical concerns related to interpretation of results when assuming the equality of pathways of NGS oversight for labs and IVD manufacturers. It is important that FDA engage with a full range of stakeholders to assure processes work across the spectrum of contexts.

## General Comments Regarding the Preliminary Discussion Draft

Accuracy and reliability, while fostering innovation and access: Personalized medicine relies on accurate and reliable determination of clinically relevant individual patient information. Yet, future investment and technological advancement depend on clear, predictable oversight processes that are not overly burdensome. PMC encourages FDA to consider risk-based oversight that appropriately fosters innovation and allows timely access to new personalized medicine information while ensuring accuracy and reliability.

Incorporating new scientific discovery: NGS oversight should be flexible in a way that allows it to keep pace with clinical and scientific advancements. While a NGS test itself may evolve gradually, the clinical application of the information provided by the test can change quickly as additional knowledge about genomic variants and their clinical significance is discovered and published. While we cannot assume that the detection of additional variants will provide new or improved clinically actionable information, FDA should be willing to accept a reasonable level of evidence to qualify additional or expanded endpoints for clinical application. We believe that some of the considerations raised in the preliminary discussion paper may be able to foster a risk-based and flexible oversight environment, and we look forward to continuing to work with FDA as concepts are further developed.

Labeling and intended use: As concepts surrounding the oversight of NGS continue to develop, the FDA should consider how to address issues related to intended use and labeling.

Due to the nature of NGS tests involving continued laboratory development and expanding multiple variant assessment, and the fact that these tests are often not marketed as physical products in packages to which labels are readily affixed, traditional processes for labeling of medical products will often not be appropriate. Clinical laboratories should not be required to maintain labels or labeling in formats required for distributed/shipped products. A laboratory should be able to fulfill any mandatory labeling requirements solely through its online directory of services.

Also, there is an important interpretive component to NGS tests. Interpretation of a NGS-identified variant in the context of a patient's clinical presentation is a part of medical practice. It is necessary to ensure that labeling restrictions do not conflict with requirements for laboratory clinical consultation. Physician laboratory directors and laboratory medicine experts advise treating physicians about available tests, test results, and possible treatment decisions that follow testing as part of the practice of medicine and based on their medical training and expertise. This is an aspect of medical practice upon which personalized medicine depends. When discussing NGS tests, physicians and laboratory medicine experts must be able to consider options that may appear not to be part of the original stated use. This includes appropriate therapeutic and preventive treatment decisions. Furthermore, information from Investigational Use Only (IUO) NGS tests should be available to be used in the context of research to suggest potential enrollment of patients in pertinent clinical trials. As oversight mechanisms for NGS tests continue to be developed, PMC urges FDA to consider how markers of currently unknown significance that nonetheless may have the potential to help determine appropriate clinical trial participation can be efficiently incorporated into research and clinical decision-making.

Intended uses of NGS tests will differ dramatically depending on the testing context. For example, a NGS test could be targeted for a specific diagnostic application, such as the MiSeqDx Cystic Fibrosis (CF) System for comprehensive CF testing, while other NGS tests such as whole genome or exome sequencing have broader applicability. Furthermore, germ line NGS tests are likely to differ dramatically from oncology testing platforms in ways that can affect standards and subset development, variant classification systems, and actionable information. These intended use contexts need to be considered as they relate to labeling and other oversight processes.

The interpretive component of NGS tests should allow for the appropriate use of medical guidelines for interpretation and reporting of diagnostic information, like those described by the American College of Medical

Genetics (ACMG), the Actionable Genome Consortium (ACG) in Oncology, the National Comprehensive Care Network (NCCN), and other recognized medical guideline bodies. PMC also encourages FDA to consider additional recommendations and standards in clinical interpretation of NGS tests that are updated continuously, and not subject to a lag between scientific advancement and guideline updating processes.

### **Analytic Performance Assessment**

It is impractical to assess the analytic validity of every possible genetic variant that could be detected in a genomic sequence. Thus, it is important that guidelines for the assessment of NGS analytic test performance be clear, predictable, and scientific, with a subset or standards-based approach. Analytical performance assessment subsets and standards need to be developed over time in consultation with appropriate technology experts and with consideration of different testing platforms, contexts, and intended uses.

PMC appreciates FDA's efforts to engage a full range of stakeholders, including the foremost NGS technology experts, in all stages of development of NGS standards and analytic assessment processes. We will continue to encourage PMC members with content expertise to actively participate in the development process, and we will provide feedback and more detailed comments whenever possible.

### **Clinical Performance Assessment**

PMC supports the FDA's approach to the development of oversight processes that recognize modifications/additions to clinical data and leverage information in large databases to inform clinical decision-making and research. These processes could be centered on curated databases that support clinical claims. We encourage FDA to also remain open to the consideration of other options of flexible clinical assessment of variant information where the most appropriate and effective regulatory oversight may not involve curated databases. PMC also encourages FDA to consider applying the criteria discussed in the context of NGS oversight to other advanced genetic technologies. The goal is to create a fair and effective oversight system of genetic technologies that promotes personalized medicine. We believe this preliminary discussion paper is a good start.

#### Questions for Public Comment on Clinical Performance:

- 2. What are the benefits and risks to public health of the use of information from curated databases such as ClinVar/ClinGen in supporting clinical claims made by NGS tests?*

New information from databases that support clinical claims could expand the intended uses of NGS tests for detection of genomic alterations of clinical significance. This would allow for oversight mechanisms to keep pace with scientific advancement, and allow patients to have access to novel tests more rapidly while providing a new mechanism for assessing the accuracy and reliability of clinical information.

However, relevant databases may not all have equal quality of data. It is imperative that processes for accurate, consistent, streamlined, and up-to-date reporting of variant data and certification of information be put in place across databases.

- 3. Would the use of ClinVar/ClinGen or other curated databases by all test developers incentivize data sharing and provide a more efficient way to establish clinical significance for different variants? Are there other steps that should be taken to facilitate sharing of this data? Is ClinVar/ClinGen the appropriate resource for FDA to utilize? Are there other resources that FDA should consider?*

The use of databases would encourage data sharing by test developers and providers, and patients would likely be the direct beneficiaries as clinical significance and actionable interpretations of data could be developed faster.

However, there is a risk of unsubstantiated or premature clinical associations being reported in databases and/or valuable clinical information being held back for proprietary concerns, so appropriate curation processes and incentives for sharing data must be developed and installed.

ClinVar is a good example of the type of database that should be considered as these concepts are further developed, but there are many databases that could be used for this purpose. Reasonable criteria for use should be developed, but a wide net should be cast to make use of all reasonable data sources that could expedite introduction of valuable new tests.

4. *Can curation and evidence evaluation standards be constructed in a manner that would allow interested developers to create databases that could support clinical significance?*

It will be important to develop strong curation criteria and standards so that multiple valuable data sources could be used to support clinical significance.

Where possible there should be an effort to incorporate real-time observational data obtained through learning health systems with appropriate standards that assure safety, accuracy, and reliability.

5. *Can information about the clinical meaning of variants be of value to physicians and patients when there is uncertainty about the strength of the association between the variant and disease? If so, why and under what circumstances?*

*and*

6. *Can information regarding variants of unknown significance or variants with conflicting evidence regarding significance be of value to providers and patients? If so, why and under what circumstances?*

Along with strong data curation criteria, an effective and clinically useful variant classification system would need to be established. Variant classification should include a hierarchy of data based on scientific strength and risk of clinical claims, should allow for the consideration of appropriate contexts for clinical information (such as specific intended use vs. broad intended use, or oncology vs. germ line variant analysis), and should indicate important elements of clinical significance assessment such as rare or co-existent variants or if there is conflicting data regarding clinical claims.

Existing variant classification systems (ex. ACMG Variant Classification Guidelines, Myriad BRCA CDx variant classification system) can serve as examples for the development of appropriate comprehensive variant classification systems.

Any system for curation and classification of database information should include a community (patient & physician) component to assist in determining the value of information within appropriate contexts.

7. *How should FDA ensure that laboratories are accurately reporting the strength of variant-disease associations?*

Information needs to be reported consistent with scientific evidence. To ensure valid variant-disease associations, strong database curation and variant classification systems must be put in place that include consideration of quantity and quality of peer-reviewed data, clinical information (potentially including learning health systems), risk associated with the intended use, any conflicts or disputes regarding clinical associations, and the existence of co-existent variants, among other data. The review and interpretation of sequence variants generated by NGS

should involve the use of consensus derived interpretation guidelines, while Information from IUO NGS assays should be considered in the context of research to suggest potential enrollment of patients in pertinent clinical trials.

8. *How can FDA incentivize test developers and clinical laboratories to deposit their information in ClinVar to improve the ability of the community to understand the genetic basis of disease?*

PMC encourages the development of appropriate incentives to encourage sponsors to submit non-proprietary data to ClinVar or other appropriate databases.

### **Conclusions/Recommendations**

PMC recognizes and appreciates that the possibilities raised in the discussion paper represent novel thinking that would be a paradigm shift in how some diagnostic tests are conducted, interpreted, and regulated. As the agency continues to consider these concepts, there are three key overarching principles that should be recognized:

1. NGS information must be accurate and reliable
2. Patients should be assured optimal access to these state-of-the art technologies
3. It is important to continue to work with all stakeholders to develop important details on how such an oversight system would be resourced, standardized, and administered

Moving forward, we recommend that FDA revise the discussion draft to incorporate feedback from the February 20 workshop and from comments submitted to the docket. This process would help to ensure that the resulting work products reflect evolving thought and best practices. As preliminary concepts mature, FDA should release more formal documents and allow for additional and more detailed comments. We urge the agency to take the time necessary to get it right. Future investment in the field depends on clear, reasonable guidelines, which are in our power to develop now.

PMC appreciates the opportunity to provide these comments. PMC and FDA are united by a shared goal to provide patients and health care providers with safe and effective technologies that will best serve the needs of patients and the health care system. If you have any questions about the content of this letter, please contact me at [dpritchard@personalizedmedicinecoalition.org](mailto:dpritchard@personalizedmedicinecoalition.org) or (202) 787-5912. We look forward to further opportunities to provide feedback.

Sincerely yours,

/s/

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