AMA
AMERICAN MEDICAL ASSOCIATION

JAMES L. MADARA, MD
EXECUTIVE VICE PRESIDENT, CEO

ama-assn.org
t (312) 464-5000

March 20, 2015

Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Preliminary discussion paper "Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests"

Dear Commissioner Hamburg:

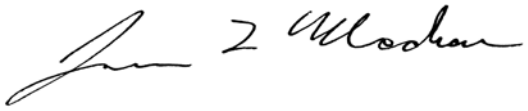
On behalf of the physician and medical student members of the American Medical Association (AMA), I appreciate the opportunity to provide comments on the U.S. Food and Drug Administration's (FDA) preliminary discussion paper "Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests." The AMA commends the FDA for its efforts to address the growing use of the next-generation sequencing platform in a forward-looking manner, and to engage stakeholders in the development of a plan for appropriate oversight. Next-generation sequencing technologies hold immense promise for improving patient care, but challenges, including those in the regulatory realm, must be addressed to ensure that the technologies are used appropriately and remain accessible to patients and their physicians.

While the AMA is in agreement with some of the approaches and proposals included in the discussion paper, it offers comments and suggested revisions to others. The AMA also underscores its strong commitment to preserving the autonomy of physicians and the practice of medicine independent of inappropriate federal government intrusion. As noted in AMA comments submitted in response to the FDA's draft guidance "Framework for Regulatory Oversight of Laboratory Developed Tests,"[1] the provision of laboratory developed testing services and procedures by physicians and laboratory medicine experts constitutes the practice of medicine, and the AMA is strongly opposed to FDA regulation of all but a small subset of such testing services and procedures. To the extent that next-generation sequencing technologies are used in laboratory developed testing services and procedures, the AMA believes that the concerns regarding accuracy and performance raised by the FDA and medical community are best addressed by modernizing and enhancing the Clinical Laboratory Improvement Amendments administered by the Centers for Medicare & Medicaid Services, rather than by potentially burdensome and duplicative FDA regulatory requirements.

[1] AMA comments on the FDA proposed guidances "Framework for Regulatory Oversight of Laboratory Developed Tests" and "Notification and Medical Device Reporting for Laboratory Developed Tests." http://download.ama-assn.org/resources/doc/washington/x-pub/fda-framework-regulatory-oversight-letter-02feb2015.pdf.

Comments on the discussion paper are offered on the following pages. The AMA looks forward to continued dialogue with the FDA on this important topic, and as always, remains committed to advocating for policies that enable physicians to practice medicine that will be most beneficial to their patients. For more information on the AMA's comments, please contact Margaret Garikes, Vice President of Federal Affairs, at 202-789-7409 or margaret.garikes@ama-assn.org.

Sincerely,



James L. Madara, MD

Enclosure

American Medical Association Comments on FDA Preliminary Discussion Paper: *Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests*

Overarching Comments

Next-generation sequencing (NGS) technologies have enabled the sequencing of large portions of the genome (in some cases the entire genome) for substantially reduced costs and timeframes than were once imaginable. NGS-based assays are carried out using instruments designed to determine genomic sequence in "massively parallel" platforms, meaning that millions of DNA fragments can be sequenced simultaneously. NGS forms the basis of large-scale clinical sequencing services such as whole genome sequencing (WGS) and whole exome sequencing (WES). It can also be used in panel-based assays to rapidly detect variants in dozens or hundreds of genes, such as those used to molecularly characterize tumors. This latter type of NGS test is currently more commonly used in the clinic than are WGS and WES, but WGS and WES are becoming more common as their benefit to patient care becomes clearer. For example, in patients with unexplained intellectual disability, WES has been used to identify new mutations and facilitate a conclusive diagnosis.

The FDA discussion paper refers to NGS as "indication-blind." The AMA disagrees with this premise and cites the many panel-based NGS services used for specific indications – Foundation Medicine's FoundationOne® tumor profiling assay is an example – as well as the many documented cases in which WGS and WES have led to diagnoses and improved care when traditional diagnostic methods had not been successful. As with other molecular laboratory services and procedures, **a physician has made a determination that an NGS-based service is indicated to inform the care of a patient in a specific clinical context.** The use of WGS and WES in asymptomatic individuals is not currently supported by clinical guidelines.

The majority of NGS-based tests are laboratory developed services and procedures. The AMA has been vocal in its belief that the FDA lacks the statutory authority to regulate laboratory developed testing services and procedures. Further, the oversight needed to ensure that tests are accurate and perform reliably lies within the Centers for Medicare and Medicaid Services, as it administers the Clinical Laboratory Improvement Amendments (CLIA). The AMA strongly believes that a modernized CLIA obviates the FDA's involvement in regulating laboratory developed testing services and procedures, including those that are NGS-based, in all but the most specialized of circumstances. Further, as it pertains to the proposals included in the discussion paper, many are similar or identical to activities that laboratories carry out as part of CLIA certification or deemed authority accreditation, such as proficiency testing by the College of American Pathologists (CAP). The AMA is concerned that a duplicative regulatory approach would be burdensome for physicians and laboratories, resulting in reduced access and higher costs for patients. The FDA has a critical role in reviewing and approving instrumentation and reagents used in NGS-based services where limited Agency resources should be focused; therefore, the AMA urges the FDA to closely study the myriad activities already undertaken by laboratories to identify those that ensure accuracy and performance and that do not need to be duplicated by FDA requirements.

Analytical Performance

One NGS-based test, even if performed for a single clinical indication, may identify dozens of clinically meaningful variants. For example, it is estimated that within a person's whole exome, more than 100 variants that are clinically actionable may be detected. Because it is impractical for laboratories to provide data on the ability of a NGS-based service, particularly WGS and WES, to accurately and reliably detect every possible variant that might exist in a genomic sequence, the AMA supports an oversight approach based on the detection of representative subsets of variants. Indeed, this is the approach that CAP uses in its proficiency testing process for NGS-based services.

Clinical Example

As a board-certified pathologist, I direct a CLIA-certified and CAP-accredited laboratory affiliated with an academic medical center. My laboratory performs WES on patients with conditions that are difficult to diagnose. To ensure that my laboratory's WES procedure is accurate and performs reliably, it undergoes CAP-administered proficiency testing for NGS. This type of proficiency testing entails the full spectrum of wet bench and bioinformatics processes for a set of test samples: sample preparation, library generation, amplification, sequencing, and data analysis, with the identification of dozens of variants of different subtypes that act as standards to validate the process. My laboratory has incorporated these proficiency testing requirements into its regular accreditation activities, and is able to manage them without disrupting the services and procedures it provides to patients. Duplicative FDA requirements would be unnecessary and could threaten my laboratory's responsibility to efficiently obtain results for patients and their treating physicians.

Additionally, the CAP-developed Molecular Pathology Checklist contains a section dedicated to NGS, setting standards for the analytic process and for bioinformatics analyses, **and is updated yearly**. The CAP Checklist and proficiency testing programs are followed by the majority of laboratories performing NGS-based services. It is therefore unnecessary and duplicative for the FDA to develop a separate system of oversight. The AMA recommends that CLIA be modernized and enhanced to include laboratory conformance to checklists and proficiency testing such as that provided by CAP. This would best ensure the quality of NGS-based tests while allowing laboratories to adhere to oversight with which they are already familiar and avoid disruptions in care that would accompany duplicative requirements.

AMA policy supports methodological standards that laboratories should meet to ensure the accuracy and performance of NGS-based services and procedures.[1] Collaborative and stakeholder-driven efforts to develop such standards already are underway, such as the Genome in a Bottle initiative, the Centers for Disease Control and Prevention's Next Generation Sequencing Standardization of Clinical Testing project (Nex-StoCT) project, and the Clinical Laboratory Standards Institute work. These efforts have formed the basis of laboratory quality standards that are being implemented as part of the CAP accreditation process. While FDA may have a role as a stakeholder in the process of standards development, the AMA believes that promulgation and enforcement of standards should be part of a modernized and enhanced CLIA and accreditation by deemed authorities like CAP. Laboratories understand the standards-based

[1] Policy H-460.905 Clinical Application of Next Generation Genomic Sequencing, AMA Policy Database.

process of CLIA certification and additional accreditation, and an enhancement of this process to ensure the quality of NGS-based services would avoid duplicative requirements and disruptions in patient care.

Clinical Performance

The AMA is a strong supporter of appropriately managed and curated databases containing health and disease information. Such databases linking genetic variant information with phenotype data have been instrumental in gene discovery and are poised to benefit patient care. AMA policy encourages laboratories to place all clinical genomic variants and the data that was used to assess the clinical significance of variants into publicly accessible databases for the benefit of patient care.[2] The AMA supports the concept that the information in databases could be one source of evidence used to assess the performance of NGS-based services and procedures. The ClinVar and ClinGen initiatives are especially promising in their potential to convey a great deal of clinical variant information. However, these databases and others are still in the early stages and contain incomplete information, and caution should be taken in making a blanket determination that all information contained in them is reliable, especially in the context of services and procedures used for patient care rather than research.

Collaborative projects have resulted in the development of guidelines for classifying the severity of a genomic variant, for example, pathogenic, likely pathogenic, unknown significance, etc. Just recently, joint consensus recommendations for the interpretation of sequence variants were released by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[3] An important component of applying guidelines to patient care is the clinical context. **Variants may be interpreted in different ways depending on the condition of the patient in question.** Even those that appear to be variants of unknown significance are meaningful in determining future testing strategies and patient management.

Clinical Example

A 60-year old woman presenting with apparent acute promyelocytic leukemia, but whose cytogenetic results suggest a different subtype, undergoes WGS on DNA extracted from her leukemic bone marrow. A novel chromosomal translocation is discovered, leading her physician team to conclude that she is not a candidate for bone marrow transplantation but rather can be treated with retinoic acid. In addition to this discovery, her WGS results indicate that she is a carrier for cystic fibrosis. This result would typically call for follow-up confirmatory testing, genetic counseling, and partner testing to determine whether offspring would be affected. However, the patient does not have children and is past childbearing years. Her physicians therefore inform her of the cystic fibrosis variant present, but conclude that follow-up testing, genetic counseling, and partner testing is not necessary. Had the patient been younger and planning to have children, a different management plan would have been indicated. Interpretation of results and appropriate application to care in the context of each clinical situation is the practice of medicine and the responsibility of every physician.

---

[2] Policy D-460.971 "Genome Analysis and Variant Identification," AMA Policy Database.

[3] ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine. Online ahead of print, March 5, 2015.

The application of physician and laboratory medicine expertise to interpret the results of a laboratory procedure that will inform patient care is the practice of medicine. **The fact that the results may have been generated using NGS-based platforms does not alter that principle.** The AMA is therefore concerned that the FDA has implied in its discussion paper that it is considering how information about variants should be conveyed. This is not the FDA's purview; rather, it is the purview of the physicians and laboratory medicine experts who are trained, licensed, and certified to provide patient care. While the FDA has a role in reviewing and approving the instrumentation and reagents purchased from manufacturers and used in the NGS process, the Agency should not have a role in the testing service and procedure itself, which includes the work of the physician-led health professional team to interpret results and apply them to patient care; this constitutes the practice of medicine and is outside of the FDA's regulatory role.

Concluding Comments

The AMA recognizes the potential of NGS to improve health outcomes, and supports oversight mechanisms that will permit NGS-based services and procedures to flourish for the benefit of patients. The AMA urges the FDA to consider the least burdensome approaches for oversight of such services and procedures. We believe these approaches are already present in the CLIA certification and deemed authority accreditation system, and that while this system could benefit from modernization and enhancement, duplicative requirements should not be instituted by the FDA. Physicians and laboratory medicine experts can best provide innovative care to patients within a regulatory system to which they are already accustomed and that has been successful in ensuring the accuracy and performance of laboratory testing and services.

American Medical Association Comments on FDA Preliminary Discussion Paper: *Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests*

Overarching Comments

Next-generation sequencing (NGS) technologies have enabled the sequencing of large portions of the genome (in some cases the entire genome) for substantially reduced costs and timeframes than were once imaginable. NGS-based assays are carried out using instruments designed to determine genomic sequence in "massively parallel" platforms, meaning that millions of DNA fragments can be sequenced simultaneously. NGS forms the basis of large-scale clinical sequencing services such as whole genome sequencing (WGS) and whole exome sequencing (WES). It can also be used in panel-based assays to rapidly detect variants in dozens or hundreds of genes, such as those used to molecularly characterize tumors. This latter type of NGS test is currently more commonly used in the clinic than are WGS and WES, but WGS and WES are becoming more common as their benefit to patient care becomes clearer. For example, in patients with unexplained intellectual disability, WES has been used to identify new mutations and facilitate a conclusive diagnosis.

The FDA discussion paper refers to NGS as "indication-blind." The AMA disagrees with this premise and cites the many panel-based NGS services used for specific indications – Foundation Medicine's FoundationOne® tumor profiling assay is an example – as well as the many documented cases in which WGS and WES have led to diagnoses and improved care when traditional diagnostic methods had not been successful. As with other molecular laboratory services and procedures, **a physician has made a determination that an NGS-based service is indicated to inform the care of a patient in a specific clinical context.** The use of WGS and WES in asymptomatic individuals is not currently supported by clinical guidelines.

The majority of NGS-based tests are laboratory developed services and procedures. The AMA has been vocal in its belief that the FDA lacks the statutory authority to regulate laboratory developed testing services and procedures. Further, the oversight needed to ensure that tests are accurate and perform reliably lies within the Centers for Medicare and Medicaid Services, as it administers the Clinical Laboratory Improvement Amendments (CLIA). The AMA strongly believes that a modernized CLIA obviates the FDA's involvement in regulating laboratory developed testing services and procedures, including those that are NGS-based, in all but the most specialized of circumstances. Further, as it pertains to the proposals included in the discussion paper, many are similar or identical to activities that laboratories carry out as part of CLIA certification or deemed authority accreditation, such as proficiency testing by the College of American Pathologists (CAP). The AMA is concerned that a duplicative regulatory approach would be burdensome for physicians and laboratories, resulting in reduced access and higher costs for patients. The FDA has a critical role in reviewing and approving instrumentation and reagents used in NGS-based services where limited Agency resources should be focused; therefore, the AMA urges the FDA to closely study the myriad activities already undertaken by laboratories to identify those that ensure accuracy and performance and that do not need to be duplicated by FDA requirements.

Analytical Performance

One NGS-based test, even if performed for a single clinical indication, may identify dozens of clinically meaningful variants. For example, it is estimated that within a person's whole exome, more than 100 variants that are clinically actionable may be detected. Because it is impractical for laboratories to provide data on the ability of a NGS-based service, particularly WGS and WES, to accurately and reliably detect every possible variant that might exist in a genomic sequence, the AMA supports an oversight approach based on the detection of representative subsets of variants. Indeed, this is the approach that CAP uses in its proficiency testing process for NGS-based services.

Clinical Example

As a board-certified pathologist, I direct a CLIA-certified and CAP-accredited laboratory affiliated with an academic medical center. My laboratory performs WES on patients with conditions that are difficult to diagnose. To ensure that my laboratory's WES procedure is accurate and performs reliably, it undergoes CAP-administered proficiency testing for NGS. This type of proficiency testing entails the full spectrum of wet bench and bioinformatics processes for a set of test samples: sample preparation, library generation, amplification, sequencing, and data analysis, with the identification of dozens of variants of different subtypes that act as standards to validate the process. My laboratory has incorporated these proficiency testing requirements into its regular accreditation activities, and is able to manage them without disrupting the services and procedures it provides to patients. Duplicative FDA requirements would be unnecessary and could threaten my laboratory's responsibility to efficiently obtain results for patients and their treating physicians.

Additionally, the CAP-developed Molecular Pathology Checklist contains a section dedicated to NGS, setting standards for the analytic process and for bioinformatics analyses, **and is updated yearly**. The CAP Checklist and proficiency testing programs are followed by the majority of laboratories performing NGS-based services. It is therefore unnecessary and duplicative for the FDA to develop a separate system of oversight. The AMA recommends that CLIA be modernized and enhanced to include laboratory conformance to checklists and proficiency testing such as that provided by CAP. This would best ensure the quality of NGS-based tests while allowing laboratories to adhere to oversight with which they are already familiar and avoid disruptions in care that would accompany duplicative requirements.

AMA policy supports methodological standards that laboratories should meet to ensure the accuracy and performance of NGS-based services and procedures.[1] Collaborative and stakeholder-driven efforts to develop such standards already are underway, such as the Genome in a Bottle initiative, the Centers for Disease Control and Prevention's Next Generation Sequencing Standardization of Clinical Testing project (Nex-StoCT) project, and the Clinical Laboratory Standards Institute work. These efforts have formed the basis of laboratory quality standards that are being implemented as part of the CAP accreditation process. While FDA may have a role as a stakeholder in the process of standards development, the AMA believes that promulgation and enforcement of standards should be part of a modernized and enhanced CLIA and accreditation by deemed authorities like CAP. Laboratories understand the standards-based

[1] Policy H-460.905 Clinical Application of Next Generation Genomic Sequencing, AMA Policy Database.

process of CLIA certification and additional accreditation, and an enhancement of this process to ensure the quality of NGS-based services would avoid duplicative requirements and disruptions in patient care.

Clinical Performance

The AMA is a strong supporter of appropriately managed and curated databases containing health and disease information. Such databases linking genetic variant information with phenotype data have been instrumental in gene discovery and are poised to benefit patient care. AMA policy encourages laboratories to place all clinical genomic variants and the data that was used to assess the clinical significance of variants into publicly accessible databases for the benefit of patient care.[2] The AMA supports the concept that the information in databases could be one source of evidence used to assess the performance of NGS-based services and procedures. The ClinVar and ClinGen initiatives are especially promising in their potential to convey a great deal of clinical variant information. However, these databases and others are still in the early stages and contain incomplete information, and caution should be taken in making a blanket determination that all information contained in them is reliable, especially in the context of services and procedures used for patient care rather than research.

Collaborative projects have resulted in the development of guidelines for classifying the severity of a genomic variant, for example, pathogenic, likely pathogenic, unknown significance, etc. Just recently, joint consensus recommendations for the interpretation of sequence variants were released by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[3] An important component of applying guidelines to patient care is the clinical context. **Variants may be interpreted in different ways depending on the condition of the patient in question.** Even those that appear to be variants of unknown significance are meaningful in determining future testing strategies and patient management.

Clinical Example

A 60-year old woman presenting with apparent acute promyelocytic leukemia, but whose cytogenetic results suggest a different subtype, undergoes WGS on DNA extracted from her leukemic bone marrow. A novel chromosomal translocation is discovered, leading her physician team to conclude that she is not a candidate for bone marrow transplantation but rather can be treated with retinoic acid. In addition to this discovery, her WGS results indicate that she is a carrier for cystic fibrosis. This result would typically call for follow-up confirmatory testing, genetic counseling, and partner testing to determine whether offspring would be affected. However, the patient does not have children and is past childbearing years. Her physicians therefore inform her of the cystic fibrosis variant present, but conclude that follow-up testing, genetic counseling, and partner testing is not necessary. Had the patient been younger and planning to have children, a different management plan would have been indicated. Interpretation of results and appropriate application to care in the context of each clinical situation is the practice of medicine and the responsibility of every physician.

---

[2] Policy D-460.971 "Genome Analysis and Variant Identification," AMA Policy Database.

[3] ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine. Online ahead of print, March 5, 2015.

The application of physician and laboratory medicine expertise to interpret the results of a laboratory procedure that will inform patient care is the practice of medicine. **The fact that the results may have been generated using NGS-based platforms does not alter that principle.** The AMA is therefore concerned that the FDA has implied in its discussion paper that it is considering how information about variants should be conveyed. This is not the FDA's purview; rather, it is the purview of the physicians and laboratory medicine experts who are trained, licensed, and certified to provide patient care. While the FDA has a role in reviewing and approving the instrumentation and reagents purchased from manufacturers and used in the NGS process, the Agency should not have a role in the testing service and procedure itself, which includes the work of the physician-led health professional team to interpret results and apply them to patient care; this constitutes the practice of medicine and is outside of the FDA's regulatory role.

Concluding Comments

The AMA recognizes the potential of NGS to improve health outcomes, and supports oversight mechanisms that will permit NGS-based services and procedures to flourish for the benefit of patients. The AMA urges the FDA to consider the least burdensome approaches for oversight of such services and procedures. We believe these approaches are already present in the CLIA certification and deemed authority accreditation system, and that while this system could benefit from modernization and enhancement, duplicative requirements should not be instituted by the FDA. Physicians and laboratory medicine experts can best provide innovative care to patients within a regulatory system to which they are already accustomed and that has been successful in ensuring the accuracy and performance of laboratory testing and services.