



AdvaMedDx
Vital Insights | Transforming Care

March 20, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: *Docket No. FDA-2014-N-2214; Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests; Public Workshop and Draft Discussion Paper*

Dear Sir or Madam:

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association (AdvaMed), we provide these comments on the Food and Drug Administration (FDA) draft discussion paper "Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests" (hereinafter "paper") and associated February 20 public workshop.

AdvaMedDx member companies produce advanced, *in vitro* diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted, policy organization that deals exclusively with issues facing *in vitro* diagnostic companies in the United States and abroad. Our membership includes manufacturers engaged in the development of innovative diagnostic technologies supporting the advancement of the public health and personalized medicine from next generation sequencing to complex multi-analyte technologies to a breadth of advanced molecular diagnostics helping deliver cutting edge care to patients worldwide.

GENERAL COMMENTS

AdvaMedDx commends the FDA (or "Agency") for the development of this proposed paper, which sets forth a highly innovative and flexible approach for evidence generation for such *in vitro* (IVD) technologies while recognizing the critical importance that tests have adequate analytical and clinical performance. We concur that as with other IVDs, an inaccurate next generation sequencing (NGS) test can present significant risk to patients and lead to patients receiving the wrong diagnosis, wrong treatment, or no treatment at all even when effective therapy is available, and can impose unnecessary costs on the healthcare system. We believe this Agency activity fits well with the Administration's precision medicine initiative and support for a modernized regulatory approach to support personalized medicine.

All in all, AdvaMedDx views this effort as a highly positive step by the FDA Office of *In Vitro* Diagnostics and Radiological Health to pursue innovative approaches to analytical and clinical validation to support advances in diagnostics technologies that hold great promise for patients and advance the quality of healthcare. Such an approach is likely to improve quality, support

predictability in test development, speed time to market, encourage innovation, and provide greater confidence in a given test result. To that end, FDA should extend wider application of these proposed approaches to other diagnostic technologies rather than limit them to NGS alone.

Examples of other appropriately applicable technologies would include polymerase chain reaction (PCR), single nucleotide polymorphism (SNP), and microarray technologies, all of which provide tremendous benefits for patients. Through this kind of innovative thinking, FDA can strike the right balance of benefit and risk and ensure appropriate oversight and timely access to new innovative tests. Furthermore, FDA should ensure consistent and equitable application of the approach to all test developers, whether laboratory or traditional IVD manufacturers. This extends to test development and modifications through the product lifecycle. While it is not clear from the proposal, any final approach should not be limited to laboratory developed tests (LDTs). If the approach is not extended to traditional IVD tests, we are concerned about new product development and the ability of laboratories to access needed IVD products.

We strongly support a standards-based approach and believe that expert standards organizations, such as the Clinical Laboratory and Standards Institute, which have access to a wide range of experts and interested parties and a history of timely and effective standards development, are well placed to develop such standards. FDA could play a role in architecture of the types of standards required in addition to overall oversight of associated platforms and tests and evaluation of performance to the standard(s). Furthermore, FDA could recognize the standard. It may also be appropriate for some of this information to be transitioned to FDA guidance documents to ensure application to future submissions. Ultimately, industry is committed to support this effort through active engagement in future expert discussions and standards development.

We believe that FDA can better leverage existing available data to support bringing new diagnostics to market. Thus, we strongly endorse FDA's proposed concept of appropriately developed and curated databases to support clinical significance. Further, we agree wholeheartedly that a one-analyte-at-a-time approach is neither appropriate nor feasible for complex multi-analyte technologies. At the same time, we suggest that such databases are overseen by disease-specific experts (e.g., Cystic Fibrosis Foundation (CF Foundation) and American Society of Clinical Oncology (ASCO)) to ensure the highest quality and most reliable data are curated. Whether it is a new or existing database, it is imperative that the databases are carefully implemented. To improve quality and quantity of information for such database(s), we recommend methods are evaluated for providing incentives to encourage sponsors after receipt of clearance or approval to voluntarily share non-proprietary data submitted to FDA for inclusion in such database(s) (e.g., ClinVar).

Of particular importance in this initiative, we support transparent and accurate information to the public related to supporting information and intended use/clinical claims; i.e., truth in labeling. This might be accomplished, for example, through providing the number of the standard or clinical reference materials so it is easily identifiable to the public among possible measures.

Again, we applaud the Agency's commitment to advancing the field through this innovative proposal and holding of the workshop last month. We appreciate the opportunity to provide our comments, which are intended to support diagnostics innovation and foster advancement of personalized medicine. Our specific comments follow with accompanying recommendations to assist FDA as it works to develop the regulatory policy moving forward. A line-numbered discussion paper is also attached to assist with review. Foremost, we strongly urge FDA to consider a more broadly applicable policy as its principles are integral to a modernized regulatory approach and should not be narrowly prescribed to one type of technology or type of developer. This important approach will go far to ensure timely access to new diagnostic innovations for the public health.

Sincerely,

/s/

Khatereh Calleja, JD
Vice President, Technology and Regulatory Affairs
Technology and Regulatory Affairs

ADVAMEDDX SPECIFIC COMMENTS

AdvaMedDx Comments on FDA Draft Discussion Paper—
Optimizing FDA’s Regulatory Oversight of Next Generation Sequencing Diagnostic Tests

Edit No. – Comment number

Change – Proposed change to the guidance

Section –Section of the guidance

Comment/Rationale – Reason for proposed change

Line No. – Guidance line number

Edit No.	Section	Line No.	Change	Comment/Rationale
1	II. FDA’s Oversight of IVDs	30	RNA needs to be added to the list of examples.	Molecular expression goes beyond DNA and FDA should seek to be as inclusive as possible when discussing nucleic acid analytes / biomarkers.
2	II. FDA’s Oversight of IVDs	35, Footer – Page 1	Definition of NGS listed here should include RNA sequencing.	Similar to previous comment, NGS technologies are being developed for analysis of both DNA and RNA.

Edit No.	Section	Line No.	Change	Comment/Rationale
3	III. NGS Tests: Challenges and Opportunities	44 - 71	Revise to include some delineation between targeted and whole genome sequencing.	FDA should include some delineation between targeted versus whole genome sequencing.
4	III. NGS Tests: Challenges and Opportunities	55 - 71	Include a description of small to mid-sized gene panel tests that are designed to interrogate targeted genes of interest.	Targeted gene panels are currently the most commonly used NGS tests in laboratories and should be included in this section.
5	IV. Exploring New Regulatory Approaches for NGS Tests	110 - 111	General comment	We strongly concur that any new approach should be designed to “assure that the public has timely access to tests that have adequate analytical and clinical performance.”
6	IV. Evaluating New Regulatory Approaches for NGS Tests	120 - 121	Revise as follows: “However, even these technologies may <u>will</u> benefit from a ...”	We agree and believe that other technologies will benefit from different approaches to capturing data related to clinical performance.
7	IV. Evaluating New Regulatory Approaches for NGS Tests	124 - 126	Definition of NGS should include RNA sequencing.	NGS technologies are being developed for analysis of both DNA and RNA.

Edit No.	Section	Line No.	Change	Comment/Rationale
8	IV.A. Analytical Performance of NGS Tests	144 - 147	General comment	It is encouraging to see FDA use a subset-based approach for establishing analytical performance of IVD tests and this should be irrespective of where the test is made.
9	IV.A. Analytical Performance of NGS Tests	148 - 157	General comment	A standards-based approach that both traditional manufacturers and labs are required to follow is a viable approach and should be implemented
10	IV.A. Analytical Performance of NGS Tests	162	General comment	We support the proposed development of methodologic quality-based standards generally (as described in lines 148-163) and specifically related to change control processes. The standards developed should allow for changes to be made regarding the product in a least burdensome manner.
11	IV. A. Analytical Performance of NGS Tests and 1. Questions for Public Comment on Analytical Performance (Q6)	169 - 172 and 186 - 189	Disease-specific standards (reference material, analytical performance requirements, and processes) should be developed.	A one-size-fits-all set of such standards will not be applicable and/or appropriate to address the diverse range of NGS assays that are being developed for clinical use.

Edit No.	Section	Line No.	Change	Comment/Rationale
12	IV. A. Analytical Performance of NGS Tests and 1. Questions for Public Comment on Analytical Performance (Q2)	175 - 176	Efforts must be made not to impose overly burdensome requirements and delay access to new product. FDA evaluation could be accomplished through evaluation of adherence to standards potentially through an abbreviated 510(k) process.	We believe risks would be minimal. FDA evaluation of analytical performance will provide greater assurance of analytical performance, transparency of test performance/common understanding of performance, predictability, and proper labeling since FDA has explicit labeling requirements that ensure critical elements of a test are addressed. However, efforts must be made not to impose overly burdensome requirements and delay access to new product.
13	IV. A. Analytical Performance of NGS Tests and 1. Questions for Public Comment on Analytical Performance (Q3 and Q4)	178 - 179 and 180 - 182	Importantly, standards employed should be broadly accepted and the approach should not be limited to NGS tests or LDTs.	Performance standards would appear to be the logical first step in the process. Having known standards for which to compare will allow patients, physicians, clinicians, and FDA to have a better understanding. Standards are likely to improve quality, predictability in test development, speed to market, encourage innovation, and provide greater confidence in a given test result. However, this approach should not be limited to NGS tests or simply LDTs. If the approach is not extended to traditional IVD tests, we are concerned about the ability of laboratories to access IVD products.

Edit No.	Section	Line No.	Change	Comment/Rationale
14	IV. A. Analytical Performance of NGS Tests and 1. Questions for Public Comment on Analytical Performance (Q6)	186 - 189	General comment	The standards described in the FDA paper appear reasonable. This approach is an improvement to the traditional paradigm and recognizes the unique features of complex multi-analyte technologies.
15	IV. A. Analytical Performance of NGS Tests and 1. Questions for Public Comment on Analytical Performance (Q8)	193 - 194	As previously discussed in our general comments, a combined approach with engagement by experts and a standards development organization is needed to develop the standard(s). FDA should be responsible for evaluating performance to the standard(s).	This will ensure appropriate expert, standards development organization, and FDA engagement.
16	IV. A. Analytical Performance of NGS Tests and 1. Questions for Public Comment on Analytical Performance (Q10)	197	This can be accomplished through a declaration of conformity. The documentation supporting the declaration could be evaluated upon inspection during routine facility audits assuming that the auditing body is inspecting to the same standards. Specifically, FDA field inspections could monitor compliance with Quality System Regulation.	

Edit No.	Section	Line No.	Change	Comment/Rationale
17	IV. B. Assessing the Clinical Performance of NGS Tests	201 - 202, 258 - 264, and 288 - 289	“Data and information may come from clinical trials, appropriately curated databases, published literature, and/or other sources of valid scientific information.”	We strongly support this approach and recognition of difference sources of valid scientific information. As previously referenced, we agree with the concept of curated databases that are reviewed and maintained by disease-specific experts (e.g., CF Foundation and ASCO). Such curated databases can lead to more consistent, well-vetted results and provide timely and cost-effective access to information that could support premarket approval and clearance. However, the database(s) will need to be carefully developed as not all databases are created equal and some may contain faulty or biased data. Thus, the standard will be important and necessary.
18	IV. B. Assessing the Clinical Performance of NGS Tests (Q7)	303 - 304	Efforts must be made to ensure that the variant sorting process is robust and will support the accurate reporting of associations. To the extent FDA monitors labeling, it will also contribute to better, more accurate reporting.	Consistent with previous discussion, it is important that databases are well curated and the approach promotes overall transparency with respect to labeling and clinical claims.

Edit No.	Section	Line No.	Change	Comment/Rationale
19	IV. B. Assessing the Clinical Performance of NGS Tests (Q11)	312 - 313 and General Comment	FDA should extend application of these proposed approaches to other diagnostic technologies rather than limit them to NGS tests alone. Furthermore, FDA should ensure consistent and equitable application of the approach to all test developers, whether laboratory or traditional IVD manufacturers.	<p>Per previous comments, FDA should consider a more broadly applicable policy as its principles are integral to a modernized regulatory approach and should not be narrowly prescribed to one type of technology or type of developer.</p> <p>If the approach is not extended to traditional IVD tests, we are concerned about new product development and the ability of laboratories to access needed IVD products.</p>

1 **Optimizing FDA’s Regulatory Oversight of Next Generation Sequencing Diagnostic**
2 **Tests—Preliminary Discussion Paper**

3 **I. Overview**

4 Next generation sequencing (NGS)¹ comprises a collection of new technologies that allow rapid
5 sequencing of large segments of an individual’s DNA and even an individual’s entire genome.
6 Reliable and accurate NGS technologies promise to accelerate “personalized” or “precision”
7 medicine, the tailoring of medical treatment to the individual characteristics of each patient.
8 Unlike other laboratory tests that typically detect a single or a defined number of substances to
9 diagnose a limited set of conditions, a single NGS test can identify thousands -- even millions --
10 of genetic variants and the results of that test could be used to diagnose or predict an individual’s
11 risk of developing many different conditions or diseases. NGS technologies are used extensively
12 in research and are rapidly entering clinical practice.

13 The capabilities of NGS tests and their rapid evolution pose challenges -- as well as opportunities
14 – for FDA in carrying out its mission to both protect and promote public health. FDA is
15 committed to drawing on the knowledge of the scientific community to help inform this
16 oversight. Appropriately-tailored oversight should foster innovation in NGS technology, allow
17 the public to have timely access to newly developed tests, and ensure that those tests are
18 accurate, reliable and clinically relevant.

19 **II. FDA’s Oversight of In Vitro Diagnostics (IVDs)**

20 Accurate and reliable diagnostic tests are a foundation of medicine. As with other IVDs, an
21 inaccurate NGS test can lead to patients receiving the wrong diagnosis,² the wrong treatment or
22 no treatment at all even when effective therapy is available, and can impose unnecessary costs on
23 the healthcare system. Inaccurate tests could cause healthy individuals to seek further testing and
24 treatment to address an erroneous belief that they have, or could develop a certain condition.
25 Conversely, inaccurate tests could lead to individuals believing that they do not have, or are at
26 low risk to develop a disease, and thus forgo screening or therapy that would benefit them. For
27 reasons such as these, FDA has regulated in vitro diagnostic tests (IVDs) for decades as part of
28 its mission to protect and promote public health.

29 IVDs are typically used in clinical laboratories, and utilize a wide range of technologies to detect
30 or measure DNA, protein, or other substances found in the human body. When FDA reviews an
31 IVD to determine whether it meets applicable safety and effectiveness requirements, and hence
32 can be marketed for clinical use, it examines whether the test is accurate and reliable (analytical
33 performance) and if the results from the test correctly identify the relevant disease or condition
34 (clinical or diagnostic performance). When FDA determines that an IVD has acceptable

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

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

41 analytical and clinical performance, the Agency clears or approves the test, and the manufacturer
42 may then legally market the device for clinical use.

43 **III.NGS Tests: Challenges and Opportunities**

44 Most IVDs detect only a single or a defined number of substances to diagnose one or several
45 specified conditions. In contrast, NGS tests are capable of detecting the over 3 billion bases in the
46 human genome, and in doing so identify the approximately 3 million genetic variants an
47 individual may have. A single use of an NGS test could enable the diagnosis of any one, or more,
48 diseases or conditions a patient presents with. NGS tests can also help to predict a patient's risk
49 for developing certain conditions. Because it is possible to sequence the whole genome, it is not
50 necessary to know what variant one wishes to identify prior to running and successfully
51 interpreting an NGS test—a concept which is very different from how traditional IVDs are used.

52 These critical differences raise certain challenges in the evaluation of NGS tests using
53 FDA's traditional regulatory approach for determining analytical and clinical performance of
54 IVDs, including:

- 55 Unlike IVDs that detect only a single or a defined number of substances to diagnose one or
56 several specified conditions, NGS tests can identify an essentially unlimited number of
57 variants based on the over 3 billion base pairs that compose the human genome. Evaluating
58 whether each data point is accurately measured would take years and thus delay the public's
59 access to the benefits of this technology.
- 60 FDA typically requires the test developer to establish that the variant identified and reported
61 is clinically meaningful to any disease or condition the test is intended for use in diagnosing.
62 The developer must submit data and/or information demonstrating the clinical significance of
63 any variant for which it wishes to make clinical claims. In many instances, NGS tests are
64 used precisely because they can routinely detect rare variants for which it may be impractical
65 for test developers to provide conclusive evidence supporting clinical significance.
- 66 The clinical relevance of many variants identified by NGS tests may have limitations because
67 of the rarity of the mutations, and their co-existence with other possible causative variants in
68 individuals with a given pathology. FDA's regulation of diagnostics is intended to ensure that
69 test results are clinically meaningful. How to communicate information regarding the
70 significance of the presence of genetic variants in a way that is understandable to physicians
71 and consumers presents challenges.

72 Although the unique features of NGS tests create regulatory challenges, these same features
73 that give rise to these challenges also provide opportunities for novel solutions:

- 74 The accumulation of data from NGS testing is enabling scientists, clinical labs, and
75 regulators to better understand NGS outputs and error modes. NGS used in research and
76 in diagnostic testing is generating a large amount of data that can be leveraged in further
77 research, clinical trials, databases, and learning health systems to further evaluate the
78 analytical and clinical performance of NGS tests.

- 79 □ The large amount of cross-genome data generated by NGS tests could allow
80 unique approaches, such as novel metrics and computational approaches, for
81 assessing test performance.
- 82 □ More generally, the cumulative generation of data through the increased use of NGS
83 testing could help spur additional research in genomics and precision medicine.

84 FDA recognizes both the regulatory challenges of evaluating NGS tests described above and the
85 unique importance of these tests to the research and clinical communities. Given its mission to
86 protect and promote public health, the Agency has worked for several years to implement
87 efficient and appropriate oversight of these tests, with the goal of assuring safety and
88 effectiveness while enabling innovation in the field and supporting the advancement of precision
89 medicine. FDA has hosted several public workshops examining various aspects of NGS,
90 beginning in 2011, and has interacted extensively with scientists and other subject matter experts
91 at conferences and in other professional venues. FDA personnel have also participated in
92 developing standards and tools for the scientific community such as the Next Generation
93 Sequencing: Standardization of Clinical Testing (Nex-StoCT) Workgroup and the Genome in a
94 Bottle Consortium. In 2013, FDA cleared the first NGS instrument as well as two NGS tests for
95 cystic fibrosis. In doing so, the Agency focused on how to use representative variants to assess
96 the analytical performance of the instrument, and the use of aggregated publically available data
97 to support the clinical relevance of variants in the CFTR gene.

98 The challenges and opportunities described above are now presenting themselves as realities
99 because of the critical mass of genomic data that has been accumulated by researchers and
100 clinicians. For this reason, FDA is now exploring new regulatory approaches that will enable the
101 Agency to provide appropriate oversight, in a way that is more suitable to the complexity and
102 data-richness of this new technology, to assure that NGS tests have adequate analytical and
103 clinical performance. Appropriate oversight of NGS testing may help improve the validity and
104 comparability of genomic data, and in doing so, could improve the quality of the evidence base
105 used by scientists when designing studies and computational strategies and in interpreting
106 research results. Instituting appropriate oversight is therefore necessary both to assure safe and
107 effective tests and to advance FDA’s mission of facilitating innovation to benefit public health,
108 particularly in the area of precision medicine.

109 **IV. Exploring New Regulatory Approaches for NGS Tests**

110 FDA recognizes that any new approach to regulating NGS tests should be designed to assure that
111 the public has timely access to tests that have adequate analytical and clinical performance. As
112 mentioned above, the very features of NGS that pose challenges to evaluating test performance
113 also present the possibility of novel solutions.

114 In this request for public input, FDA is considering new regulatory approaches only for NGS
115 tests because this technology allows broad and indication-blind testing and is capable of
116 generating vast amounts of data, both of which present issues that traditional regulatory
117 approaches are not well-suited to address. Other technologies capable of detecting genetic
118 variation, including but not limited to PCR and SNP arrays, are generally designed to capture
119 predefined data points that are known in advance of testing, and therefore are more suited to
120 regulation under traditional approaches. However, even these technologies may benefit from a

121 different approach for capturing data related to clinical performance. Furthermore, these new
122 approaches would not apply to the manufacturing of components of NGS tests (e.g., stand-alone
123 software, instrumentation, reagents).

124 For the purposes of addressing the questions presented below, an NGS test is defined as a
125 human DNA sequencing assay performed on a particular NGS instrument (e.g., MiSeqDx) with
126 a workflow defined by standard operating procedures that specify all materials and procedures.
127 This includes all steps from defining the patient sample type and method of DNA extraction to
128 computational processing of sequencing data, and, if offered, any portion of interpretation of the
129 clinical meaning of individual variants identified in that patient that is performed within the test
130 system (including software) rather than by a healthcare professional. The intended use of the
131 NGS test may be specific for certain types of specimens, patient populations, etc., but does not
132 necessarily include any claims about the clinical relevance of specific variants.

133 **A. Analytical Performance of NGS Tests**

134 FDA has authorized the marketing of one NGS instrument (Illumina MiSeqDxTM) and its
135 universal sequencing reagents³, and two accompanying assays for the diagnosis of cystic fibrosis
136 (Illumina MiSeqDxTM Cystic Fibrosis 139 Variant and Clinical Sequencing Assays). In doing so,
137 FDA and the developer worked together to successfully address some of the challenges noted
138 above. For instance, because it was impractical to provide data on the ability of the instrument to
139 accurately and reliably detect every possible variant that might exist in a genomic sequence,
140 analytical test performance for the MiSeqDx system was demonstrated for a representative subset
141 of types of variants in various sequence contexts. Demonstrating adequate analytical performance
142 for this subset provided reasonable assurance that the test would be able to successfully identify
143 relevant variants in the genome without requiring the company to submit data for every possible
144 variant the test could identify. FDA plans to continue to use this subset-based approach when
145 evaluating the analytical performance of NGS platforms, but is considering novel and efficient
146 approaches for establishing analytical performance for specific NGS tests developed using FDA
147 cleared or approved components in clinical diagnostic laboratories.

148 One such approach would be to promote the development of methodologic quality-based
149 standards⁴ that laboratories could meet as a means to demonstrate analytical performance of any
150 NGS test that is developed by the lab. Such standards could:

- 151 Define the technical metrics of NGS data quality and test performance (e.g., error rates,
152 coverage, depth) that must be satisfied no matter how NGS is performed;⁵
- 153 Include computational approaches to establish analytical performance;
- 154 Provide guidelines for quality systems that laboratories must have in place to develop
155 NGS tests;
- 156 Provide current best practices for quality assurance and control in NGS sequencing, and
157 specify requirements for proficiency testing;

158 ³ FDA also cleared the MiSeqDxTM Universal Kit 1.0 for use with the platform.

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

161 ⁵ Alternatively there could be a different standard for each test, technology, and/or intended use.

162 □ Provide for change control processes that would accommodate changes to technology
163 while retaining accurate and reliable performance.

164 Standards could be created by an *ad hoc* committee of experts, FDA, or through a Standards
165 Development Organization (SDO), such as the Clinical Laboratory and Standards Institute
166 (CLSI), or a combination of the above. If the standards were created by an SDO, FDA would
167 review and recognize those standards using its already established Standards Programs. FDA is
168 seeking public comment on various aspects of this approach.

169 FDA would like specific feedback with regard to: (1) value of a standards-based approach to
170 regulatory review of NGS tests (2) content of standards to be developed that will assure that
171 conformity to the standard will assure test accuracy and reliability, (3) who should develop such
172 standards, and (4) appropriate mechanisms to ensure compliance.

173 **1. Questions for Public Comment on Analytical Performance**

- 174 1. How are labs currently developing NGS tests and assessing their analytical performance?
- 175 2. What are the benefits and risks to public health of having FDA independently evaluate
176 the analytical performance of NGS tests and/or platforms using data submitted by the
177 developer on an agreed upon subset of data points for the test?
- 178 3. What are the benefits and risks to public health of a standards-based approach to
179 regulating NGS analytical performance?
- 180 4. Would a standards-based approach limited to NGS tests that use FDA cleared or
181 approved components encourage continued development and consumer access to NGS
182 tests with appropriate analytical performance?
- 183 5. To what extent could computational approaches be used to assess analytical
184 performance? If possible, who should develop such approaches, how could FDA
185 facilitate their development, and how could they be validated?
- 186 6. Are the concepts for standards outlined above adequate to ensure that NGS tests have
187 appropriate analytical performance? If not, what else should be included? Alternatively,
188 are some of the concepts for standards listed above unnecessary, and if so, which ones
189 and why?
- 190 7. How should changes or advances in technology be managed utilizing a standards-based
191 approach? What types of changes in technology pose the most concern and what are the
192 best standards to address those concerns?
- 193 8. Who should develop the standards: FDA, an *ad hoc* committee of experts, a Standards
194 Development Organization, others, or a combination of these approaches?
- 195 9. What measures should be put in place to monitor progress and impact, both positive and
196 negative, if a standards-based approach were adopted?
- 197 10. How should conformity with standards be assessed?

198 **B. Assessing the Clinical Performance of NGS Tests**

199 Clinical or diagnostic claims for particular tests are typically evaluated by FDA based on a
200 sponsor’s submission of adequate data or information in a premarket application for their
201 device or device platform. Data and information may come from clinical trials, appropriately
202 curated databases, published literature, and/or other sources of valid scientific evidence. When
203 clearing Illumina’s NGS-based cystic fibrosis assays, FDA and the developer addressed the
204 challenge of providing evidence for the clinical relevance of rare variants by allowing the
205 developer to make use of a well-curated third party database consisting of evidence from
206 multiple sources to establish clinical significance⁶, as an alternative to conducting a new study
207 or using existing literature. The two cystic fibrosis assays that were cleared differ in their
208 indications and approaches to clinical performance:

- 209 The variant panel assay reports only a discrete number of variants with established
210 clinical significance.⁷
- 211 The clinical sequencing assay reports any variant in the cystic fibrosis gene,
212 regardless of whether clinical significance of the specific variant is known, and
213 therefore has more limited indications for use.⁸

214 FDA is interested in public input on how this approach could be applied more broadly to enable
215 access to timely, accurate, and reliable genomic information in a manner that is meaningful for
216 clinical decision-making.

217 **1. Leveraging Genetic Databases to Evaluate Clinical Performance**

218 FDA believes that it could use high quality curated genetic databases that provide information on
219 genetic variants and their association with disease to better establish the clinical performance of
220 NGS tests by providing evidence about such associations and the strength of that evidence. FDA
221 is particularly interested in those databases that actively engage the scientific community to
222 provide ongoing evidence assessment using the best available data at any given time (e.g.,
223 continuous learning). FDA has initiated a dialogue with the National Institutes of Health (NIH)
224 aimed at determining whether the data curated by the ClinGen program⁹ and deposited in
225 ClinVar¹⁰ could be leveraged to support clinical significance for variants detected by NGS tests.
226 ClinVar is a freely accessible, public archive of reports of the relationships among human
227 variations and phenotypes annotated with supporting evidence. ClinVar facilitates access to and
228 communication about the relationships asserted between human variation and observed health
229 status, and the history of that interpretation. ClinGen is an NIH-funded effort dedicated to expert
230 evaluation of research data and the data from the hundreds of thousands of clinical genetics tests

231 ⁶ Clinical and Functional Translation of CFTR; www.cftr2.org

232 ⁷ Illumina MiSeqDx™ CF139-Variant Assay (CF139) 510(k) Substantial Equivalence Determination –
233 Decision Summary (K124006); http://www.accessdata.fda.gov/cdrh_docs/reviews/K124006.pdf

234 ⁸ Illumina MiSeqDx™ Cystic Fibrosis Clinical Sequencing Assay link - 510(k) Substantial Equivalence
235 Determination – Decision Summary (K132750); http://www.accessdata.fda.gov/cdrh_docs/reviews/K132750.pdf

236 ⁹ ClinGen is an NIH-funded resource for the development and implementation of a framework for evaluating the
237 clinical validity of human genomic variants; <http://iccg.org/about-the-iccg/clingen/>.

238 ¹⁰ ClinVar is an NIH-supported database containing human variants and evidence supporting their relationship to
239 phenotypes; <http://www.clinvar.com/>.

240 being performed each year to determine which variants are most relevant to patient care. NIH has
241 been engaged with the clinical and scientific communities to establish criteria for the strength of
242 association between genetic variants and a disease that exceeds a minimum standard to assure
243 there is credible evidence of some association. Once the ClinGen process has been applied to the
244 evidence on variant-disease association, it would issue a conclusion regarding the levels and
245 adequacy of the evidence to support a valid association between a genetic variant and a
246 disease/condition. The ClinGen process allows the strength of the variant-disease link to be
247 updated as new evidence is generated and entered into ClinVar.

248 FDA has focused on the use of ClinVar and ClinGen because they are publically accessible,
249 transparent, scalable, and evidence is continually curated by the scientific community using the
250 most current data available. However, other databases could meet the same needs, provided that
251 they met certain criteria for curation, versioning, updating, and other processes. For example,
252 FDA utilized a database to support clearance of the Illumina cystic fibrosis assays that was
253 developed and supported in part by a disease advocacy foundation. The Agency is seeking public
254 comment on the use of other curated databases to support clinical claims for genetic and genomic
255 diagnostic tests, as well as on creating a public process based on important curation criteria so
256 that other databases could be recognized as having sufficient quality to support clinical
257 significance for variants detected by NGS tests.

258 In considering the concept of using externally-generated evidence assessments to support clinical
259 performance, FDA believes that it should participate with NIH and the scientific community in
260 the evidence assessment process, with a goal of streamlining steps the Agency would need to
261 utilize this factual information in its risk-benefit assessments for potential clinical claims.
262 Ultimately the Agency's goal is to allow test developers to leverage FDA-recognized evidence-
263 based assessments of the clinical significance of genetic variants. This would minimize the need
264 for sponsors to generate their own data in order to support a premarket submission to the FDA.

265 This approach would introduce a number of efficiencies, which, ideally, would provide providers
266 and patients with better clinical understanding of the relevance of a larger number of variants
267 much more rapidly than would occur without a shared database and centralized evidence
268 assessment. It would facilitate data sharing and common use of information that has previously
269 existed in silos, and it would allow multiple developers to rely on the same evidence supporting
270 clinical relevance, rather than have each developer generate or aggregate the evidence
271 individually.

272 **2. Whether and How to Communicate Information About Less Well-Understood Variants**

273 The evidence for association of many genetic variants and particular diseases is limited because
274 of the rarity of the variant, or its coexistence with other variants in the presence of a given
275 pathology. Some stakeholders have asserted that information regarding genetic variants for
276 which there is not sufficient evidence to demonstrate clear clinical significance, but for which
277 there is evidence to establish a likely association, may have some value to physicians and their
278 patients in clinical decision-making in certain circumstances. FDA would like to further explore
279 this concept, and is interested in public comment about: 1) the value of conveying information
280 about genetic variants for which there is limited evidence of clinical significance, 2) whether
281 some caveat as to the limitations of the available data may be needed, and, 3) if this can be of
282 value, how and under what circumstances the information should be conveyed, to assure the

283 information is effectively communicated, the benefit to medical decision-making is maximized,
284 and risks to patients are minimized.

285 **3. Questions for Public Comment on Clinical Performance**

- 286 1. What are current practices for clinical interpretation of variant information from
287 NGS tests?
- 288 2. What are the benefits and risks to public health of the use of information from curated
289 databases such as ClinVar/ClinGen in supporting clinical claims made by NGS tests?
- 290 3. Would the use of ClinVar/ClinGen or other curated databases by all test developers
291 incentivize data sharing and provide a more efficient way to establish clinical
292 significance for different variants? Are there other steps that should be taken to facilitate
293 sharing of this data? Is ClinVar/ClinGen the appropriate resource for FDA to utilize? Are
294 there other resources that FDA should consider?
- 295 4. Can curation and evidence evaluation standards be constructed in a manner that would
296 allow interested developers to create databases that could support clinical significance?
- 297 5. Can information about the clinical meaning of variants be of value to physicians
298 and patients when there is uncertainty about the strength of the association between
299 the variant and disease? If so, why and under what circumstances?
- 300 6. Can information regarding variants of unknown significance or variants with
301 conflicting evidence regarding significance be of value to providers and patients? If so,
302 why and under what circumstances?
- 303 7. How should FDA ensure that laboratories are accurately reporting the strength of
304 variant-disease associations?
- 305 8. How can FDA incentivize test developers and clinical laboratories to deposit their
306 information in ClinVar to improve the ability of the community to understand the
307 genetic basis of disease?
- 308 9. What controls should be in place, if any, for laboratories who wish to implement their
309 own interpretive process, rather than relying on FDA-recognized evidence assessments?
- 310 10. What measures should be put in place to monitor progress and impact, both positive
311 and negative, of the proposed use of well curated databases?
- 312 11. What other options should FDA consider to assure that the clinical significance
313 of variants reported by NGS tests is accurate?

314 **V. Conclusion**

315 NGS tests are unique among existing IVDs in the amount of data that can be generated, the lack
316 of an *a priori* definition of what will be detected, and the number of clinical interpretations that
317 can be made from a single patient sample. In order to continue to support the development of

318 useful medical information, FDA believes the most efficient possible approaches to regulating
319 NGS tests should be considered. Among the possibilities, a standards-based approach to
320 analytical performance of NGS tests and the use of centralized curated databases containing up-
321 to-date evidence to support clinical performance are under discussion. Because stakeholder
322 feedback is important as FDA considers new approaches, the Agency will hold a public meeting
323 on February 20, 2015, and open a public docket to accept comments on these approaches and
324 the questions raised above. After review of input gathered by these efforts, FDA will determine
325 the types of changes, if any, that it should initiate with respect to its oversight to NGS tests, and
326 communicate its findings and conclusions to the public.