



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2016-D-1270]

Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing-Based In Vitro Diagnostics Intended to Aid in the Diagnosis of Suspected Germline Diseases; Guidance for Stakeholders and Food and Drug Administration Staff; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of the final guidance entitled "Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)--Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases; Guidance for Stakeholders and Food and Drug Administration Staff." FDA's vision is that NGS-based tests can be developed, validated, and offered for clinical use through a process that leverages appropriate standards, quality systems controls, and community assessment of clinical validity to streamline the premarket review process. This guidance provides recommendations for designing, developing, and establishing analytical performance for NGS-based tests used for whole exome human DNA sequencing (WES) or targeted human DNA sequencing intended to aid in the diagnosis of symptomatic individuals with suspected germline diseases or other conditions. These recommendations are based on FDA's understanding of the tools and

processes needed to run an NGS-based test along with the design and analytical validation considerations appropriate for such tests.

DATES: The announcement of the guidance is published in the *Federal Register* on **[INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2016-D-1270 for "Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases; Guidance for Stakeholders and Food and Drug Administration Staff." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made

publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential."

Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

An electronic copy of the guidance document is available for download from the internet. See the SUPPLEMENTARY INFORMATION section for information on electronic access to the guidance. Submit written requests for a single hard copy of the guidance document entitled "Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases; Guidance for Stakeholders and Food and Drug Administration Staff" to the Office of the Center Director, Guidance and Policy Development, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 5431, Silver Spring, MD 20993-0002, or the Office of Communication, Outreach, and Development, Center for Biologics Evaluation and Research, Food and Drug

Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128 Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your request.

FOR FURTHER INFORMATION CONTACT: Zivana Tezak, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4544, Silver Spring, MD 20993-0002, 301-796-6206; or OIRPMGroup@fda.hhs.gov; or Adam Berger, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4547, Silver Spring, MD 20993-0002, 240-402-1592; or OIRPMGroup@fda.hhs.gov; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is committed to implementing a flexible and adaptive regulatory approach to the oversight of NGS-based tests, which will foster innovation and simultaneously assure that patients have access to accurate and meaningful test results. FDA held two public workshops on this issue: "Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests Public Workshop" held on February 20, 2015, and "Standards Based Approach to Analytical Performance Evaluation of Next Generation Sequencing In Vitro Diagnostic Tests" held on November 12, 2016.

This guidance document provides recommendations for designing, developing, and establishing analytical validity of NGS-based tests used for WES or targeted human DNA sequencing intended to aid in the diagnosis of individuals with suspected germline diseases or other conditions (hereinafter referred to as "NGS-based tests for germline diseases" or "NGS-

based tests"). It also outlines considerations for possibly classifying certain NGS-based tests for germline diseases in class II and exempting them from premarket notification requirements.

These recommendations should be used as guidelines for test developers for premarket submissions. However, the longer term goal is for these recommendations to form the basis for standards that FDA could recognize or for special controls and/or conditions for premarket notification (510(k)) exemption. FDA is also issuing a guidance entitled "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics" which is being issued concurrently elsewhere in this issue of the *Federal Register*.

On July 8, 2016, FDA announced a draft guidance in the *Federal Register* (81 FR 44614) and made available for public comment. The comment period closed on October 6, 2016. FDA reviewed and considered all public comments received and revised the guidance, as appropriate.

II. Significance of Guidance

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on considerations for design, development, and analytical validation of NGS-based IVDs used to aid in the diagnosis of suspected germline diseases. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. This guidance is not subject to Executive Order 12866.

III. Electronic Access

Persons interested in obtaining a copy of the guidance may do so by downloading an electronic copy from the internet. A search capability for all Center for Devices and Radiological Health guidance documents is available at <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default>

lt.htm. This guidance document is also available at <https://www.regulations.gov>. Persons unable to download an electronic copy of "Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases; Guidance for Stakeholders and Food and Drug Administration Staff" may send an email request to CDRH-Guidance@fda.hhs.gov to receive an electronic copy of the document. Please use the document number 16009 to identify the guidance you are requesting.

IV. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 807, subpart E, regarding premarket notification submissions, have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 801 and 21 CFR 809.10, regarding labeling, have been approved under OMB control number 0910-0485; the collections of information in 21 CFR part 814, subparts A through E, regarding premarket approval, have been approved under OMB control number 0910-0231; the collections of information in 21 CFR part 820, regarding the quality system regulation, have been approved under OMB control number 0910-0073; and the collections of information in the guidance document "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" have been approved under OMB control number 0910-0756.

Dated: April 9, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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