April 11, 2018

IDx, LLC
% Janice Hogan
Regulatory Counsel
Hogan Lovells US LLP
1735 Market Street, Suite 2300
Philadelphia, Pennsylvania 19103

Re: DEN180001
Trade/Device Name: IDx-DR
Regulation Number: 21 CFR 886.1100
Regulation Name: Retinal diagnostic software device
Regulatory Class: Class II
Product Code: PIB
Dated: January 12, 2018
Received: January 12, 2018

Dear Janice Hogan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the IDx-DR, a prescription device under 21 CFR Part 801.109 with the following indications for use:

> IDx-DR is indicated for use by health care providers to automatically detect more than mild diabetic retinopathy (mtmDR) in adults diagnosed with diabetes who have not been previously diagnosed with diabetic retinopathy. IDx-DR is indicated for use with the Topcon NW400.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the IDx-DR, and substantially equivalent devices of this generic type, into Class II under the generic name retinal diagnostic software device.

FDA identifies this generic type of device as:

> **Retinal diagnostic software device**. A retinal diagnostic software device is a prescription software device that incorporates an adaptive algorithm to evaluate ophthalmic images for diagnostic screening to identify retinal diseases or conditions.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This new law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of

the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register classifying the device type.

On January 12, 2018, FDA received your De Novo requesting classification of the IDx-DR. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the IDx-DR into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the De Novo request, FDA has determined that, for the previously stated indications for use, the IDx-DR can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Table 1 – Identified Risks to Health and Mitigation Measures

Identified Risk	**Mitigation Measures**
False positive results leading to additional unnecessary medical procedures • Diagnostic algorithm failure • Software failure	Clinical performance testing; Software verification, validation, and hazard analysis; and Protocol for technical specification changes
False negative results leading to delay of further evaluation or treatment • Diagnostic algorithm failure • Software failure	Clinical performance testing Software verification, validation, and hazard analysis; Protocol for technical specification changes; and Labeling
Operator failure to provide images that meet input quality specifications	Labeling, Training, and Human factors validation testing

In combination with the general controls of the FD&C Act, the retinal diagnostic software device is subject to the following special controls:

1. Software verification and validation documentation, based on a comprehensive hazard analysis, must fulfill the following:

    a. Software documentation must provide a full characterization of technical parameters of the software, including algorithm(s).

    b. Software documentation must describe the expected impact of applicable image acquisition hardware characteristics on performance and associated minimum specifications.

c. Software documentation must include a cybersecurity vulnerability and management process to assure software functionality.

d. Software documentation must include mitigation measures to manage failure of any subsystem components with respect to incorrect patient reports and operator failures.

2. Clinical performance data supporting the indications for use must be provided, including the following:

a. Clinical performance testing must evaluate sensitivity, specificity, positive predictive value, and negative predictive value for each endpoint reported for the indicated disease or condition across the range of available device outcomes.

b. Clinical performance testing must evaluate performance under anticipated conditions of use.

c. Statistical methods must include the following:

i. Where multiple samples from the same patient are used, statistical analysis must not assume statistical independence without adequate justification.
ii. Statistical analysis must provide confidence intervals for each performance metric.

d. Clinical data must evaluate the variability in output performance due to both the user and the image acquisition device used.

3. A training program with instructions on how to acquire and process quality images must be provided.

4. Human factors validation testing that evaluates the effect of the training program on user performance must be provided.

5. A protocol must be developed that describes the level of change in device technical specifications that could significantly affect the safety or effectiveness of the device.

6. Labeling must include:

a. Instructions for use, including a description of how to obtain quality images and how device performance is affected by user interaction and user training.

b. The type of imaging data used, what the device outputs to the user, and whether the output is qualitative or quantitative.

c. Warnings regarding image acquisition factors that affect image quality.

d. Warnings regarding interpretation of the provided outcomes, including:

i. A warning that the device is not to be used to screen for the presence of diseases or conditions beyond its indicated uses.

ii. A warning that the device provides a screening diagnosis only and that it is critical that the patient be advised to receive follow-up care.
iii. A warning that the device does not treat the screened disease.

e. A summary of the clinical performance of the device for each output, with confidence intervals.

f. A summary of the clinical performance testing conducted with the device, including a description of the patient population and clinical environment under which it was evaluated.

In addition, this is a prescription device and must comply with 21 CFR 801.109.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the retinal diagnostic software device they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD&C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD&C Act); 21 CFR 1000-1050.

A notice announcing this classification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the De Novo request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Ronald Schuchard at 240-402-6129.

Sincerely,

Angela C. Krueger -S

Angela C. Krueger
Deputy Director, Engineering and Science Review (Acting)
Office of Device Evaluation
Center for Devices and Radiological Health