August 3, 2020

Eyenuk, Inc
Kaushal Solanki, Ph.D.,
Chief Executive Officer
5850 Canoga Ave. Suite 250
Los Angeles, California 91367

Re: K200667
Trade/Device Name: EyeArt
Regulation Number: 21 CFR 886.1100
Regulation Name: Retinal diagnostic software device
Regulatory Class: Class II
Product Code: PIB
Dated: June 30, 2020
Received: June 30, 2020

Dear Dr. Solanki:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the 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) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). 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 (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Elvin Ng
Assistant Director
DHT1A: Division of Ophthalmic Devices
OHT1: Office of Ophthalmic, Anesthesia,
Respiratory, ENT and Dental Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K200667

Device Name
EyeArt

Indications for Use *(Describe)*
EyeArt is indicated for use by healthcare providers to automatically detect more than mild diabetic retinopathy and vision-threatening diabetic retinopathy (severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy and/or diabetic macular edema) in eyes of adults diagnosed with diabetes who have not been previously diagnosed with more than mild diabetic retinopathy. EyeArt is indicated for use with Canon CR-2 AF and Canon CR-2 Plus AF cameras in both primary care and eye care settings.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

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510(k) SUMMARY

Eyenuk's EyeArt

Submitter

Eyenuk, Inc.
5850 Canoga Ave., Suite 250
Los Angeles, CA, 91367

Phone: +1 (818) 835-3585

Contact Person: Kaushal Solanki

Date Prepared: August 3, 2020

Name of Device: EyeArt

Classification Name: Retinal diagnostic software device

Regulatory Class: Class II

Regulation: 21 CFR 886.1100

Product Code: PIB

Legally Marketed Predicate Device

Trade name of the device: IDx-DR

Manufacturer's Name: IDx LLC

De Novo Number: DEN180001

A. Intended Use / Indications for Use

EyeArt is indicated for use by healthcare providers to automatically detect more than mild diabetic retinopathy and vision-threatening diabetic retinopathy (severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy and/or diabetic macular edema) in eyes of adults diagnosed with diabetes who have not been previously diagnosed with more than mild diabetic retinopathy. EyeArt is indicated for use with Canon CR-2 AF and Canon CR-2 Plus AF cameras in both primary care and eye care settings.

B. Device Description

EyeArt is a software as a medical device that consists of several components – Client, Server, and Analysis Computation Engine – as presented in **Figure 1** below.

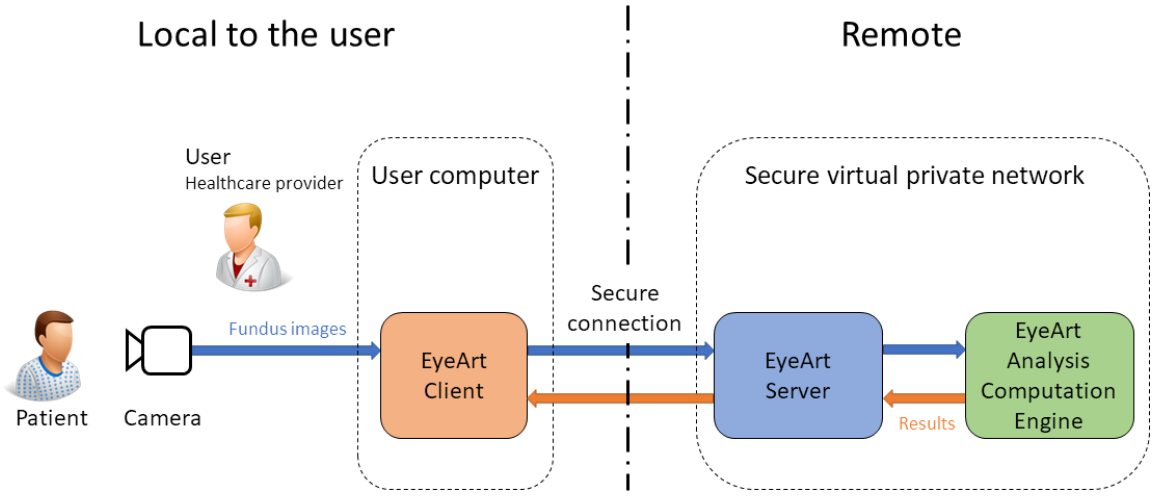

Figure 1: EyeArt components: Client, Server, and Analysis Compute Engine.

A retinal fundus camera, used to capture retinal fundus images of the patient, is connected to a computer where the EyeArt Client software is installed. The EyeArt Client software provides a graphical user interface (GUI) that allows the EyeArt operator to transfer the appropriate fundus images to and receive results from the remote EyeArt Analysis Computation Engine through the EyeArt Server. The EyeArt Analysis Computation Engine is installed on remote computer(s) in a secure data center and uses artificial intelligence algorithms to analyze the fundus images and return results. EyeArt is intended to be used with color fundus images of resolution 1.69 megapixels or higher captured using one of the indicated color fundus cameras (Canon CR-2 AF and Canon CR-2 Plus AF) with 45 degrees field of view. EyeArt is specified for use with two color fundus images per eye: optic nerve head (ONH) centered and macula centered.

For each patient eye, the EyeArt results separately indicate whether more than mild diabetic retinopathy (mtmDR) and vision-threatening diabetic retinopathy (vtDR) are detected. More than mild diabetic retinopathy is defined as the presence of moderate non-proliferative diabetic retinopathy or worse on the International Clinical Diabetic Retinopathy (ICDR) severity scale and/or the presence of diabetic macular edema. Vision-threatening diabetic retinopathy is defined as the presence of severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy on the ICDR severity scale and/or the presence of diabetic macular edema. Description of EyeArt components is provided below.

- EyeArt Client: This component is installed on the computer used by the EyeArt operator (working under supervision of a healthcare provider). It allows the operator to transfer images to the EyeArt Analysis Computation Engine and receive results. Its functioning requires an internet connection. If images from a patient encounter cannot be analyzed,

due to poor image quality or due to lack of all required image fields, feedback is provided to the operator to help successfully obtain results upon resubmission.

- EyeArt Server: This component provides an interface that securely handles incoming requests and securely stores user information including images and results. It enables the EyeArt Client to use the EyeArt Analysis Computation Engine through an application programming interface (API).
- EyeArt Analysis Computation Engine: This component analyzes the images to determine exam quality and detect mtmDR and vtDR. It consists of an ensemble of clinically aligned machine learning (deep learning) algorithms.

C. Non-clinical Testing

EyeArt (software version v2.1.0) was identified as having a major level of concern as defined in the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices."

Verification and validation activities at unit, integration, and system level were performed. In all instances, EyeArt functioned as intended and results observed were as expected (i.e. all specifications were met).

Comprehensive risk analysis has been conducted for EyeArt with identification and detailed characterization of the hazards including their causes and severity. Adequate risk control measures have been designed and implemented to mitigate all identified hazards to acceptable levels.

EyeArt also implements comprehensive cybersecurity measures for data confidentiality, data integrity, and data and service availability. Designed to meet industry standard cybersecurity best practices, EyeArt ensures that data remains secure (with encryption during transit and at rest) and private (with authentication and authorization protocols enabling access).

EyeArt has been designed to provide results that are aligned with the clinical practice recommendations for the ophthalmic care of patients with diabetes and has been developed in a clinically aligned framework.

A change protocol was also submitted, to allow for updates and improvements to EyeArt while ensuring that the changes do not introduce risks that adversely affect the safety and effectiveness of the device for its intended use.

D. Clinical Testing

1. Overview

EyeArt was validated in a prospective, multi-center pivotal clinical trial (ClinicalTrials.gov ID NCT03112005). A total of 942 subjects were consented of which 915 subjects met study

eligibility criteria. The study was designed to support a *De Novo* submission since a predicate device did not exist when the EyeArt clinical trial was launched. To better align the analysis population with the proposed intended use population, analyses were presented on 655 participants after excluding subjects who did not meet certain additional prespecified criteria (e.g., subjects 21 years old or younger). The 655 participants were enrolled in the study at 11 US study sites that included primary care centers and general ophthalmology centers. The participants were further divided into two cohorts: one for subjects enrolled during a period of sequential enrollment only (235 subjects, with 45 enrolled at primary care sites and 190 enrolled at ophthalmology sites) and the second enrolled during a period when procedures allowed sequential as well as enriched enrollment (420 subjects, with 335 enrolled at primary care sites and 85 enrolled at ophthalmology sites). The performance of EyeArt was evaluated against a reference standard determined by experienced and certified graders at the Fundus Photography Reading Center (FPRC) per the Early Treatment for Diabetic Retinopathy Study severity (ETDRS) scale on dilated 4-wide field stereo fundus imaging by FPRC certified photographers. The subject disposition is shown in **Figure 2** below.

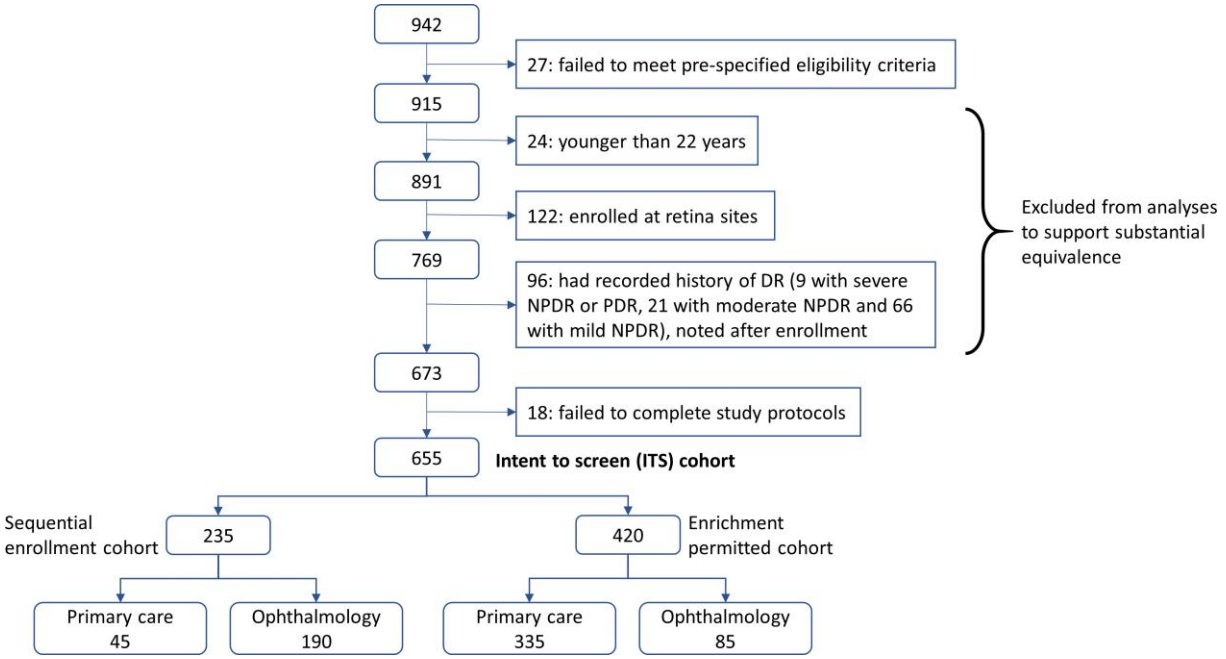

Figure 2: Subject disposition and cohorts used for analyses to support substantial equivalence.

2. Study Design and Methods

The target population of the EyeArt pivotal clinical trial analysis was asymptomatic persons aged 22 years and older who were diagnosed with diabetes and not diagnosed with more than mild diabetic retinopathy. The enrollment was conducted sequentially for the first several months of the study ("sequential enrollment" period). In order to increase the likelihood of enrolling patients with more severe levels of diabetic retinopathy (DR), for a portion of the study, sites were permitted to preferentially enroll subjects who met specific eligibility criteria based on

duration of diabetes, insulin dependence (for subjects with type-2 diabetes), or hemoglobin A1C (HbA1c) levels. During this period ("enrichment-permitted" period), sites could also enroll scheduled subjects sequentially. In other words, during this period, enrichment was permitted but not required.

During the study visit, subjects underwent 2-field retinal photography by a trained operator for processing by EyeArt. Subjects then underwent dilated 4-wide field stereo retinal photography by an FPRC certified operator for the clinical reference standard. The dilated four wide-field stereo-image sets were independently reviewed and graded by certified graders at FPRC, to determine the severity of diabetic retinopathy (DR) and diabetic macular edema (DME) according to the ETDRS severity scale. Each subject's images were graded independently by 2 experienced and certified graders and in case of significant differences (determined using pre-specified significance levels) in the 2 independent gradings, a more experienced adjudication grader graded the same images. Throughout the study, the graders and study staff at the FPRC were masked to the patient history and EyeArt results. The FPRC grading was used to determine the clinical reference standard for subject eyes as follows for the analyses:

- Clinical reference standard for more than mild DR (mtmDR)
    - *positive* if ETDRS level was 35 or greater (but not equal to 90) or clinically significant macular edema [CSME] grade was *CSME present*
    - *negative* if ETDRS levels were 10-20 and CSME grade was *CSME absent*
    - *ungradable* if ETDRS level was 90, or CSME grade was *cannot grade* or *questionable* with ETDRS level 10-20
- Clinical reference standard for vision-threatening DR (vtDR)
    - *positive* if ETDRS level was 53 or greater (but not equal to 90) or CSME grade was *CSME present*
    - *negative* if ETDRS levels were 10-47 and CSME grade was *CSME absent*
    - *ungradable* if ETDRS level was 90, or CSME grade was *cannot grade* or *questionable* with ETDRS level 10-47

EyeArt results for each eye included detection results for more than mild DR (mtmDR) and vision-threatening DR (vtDR) and each of the mtmDR and vtDR results were *negative* or *positive*, or when sufficient-quality images were not present, *ungradable*. The EyeArt mtmDR and vtDR results for each eye were compared to the mtmDR and vtDR clinical reference standard based on the FPRC grading.

3. Study Population and Demographics

In **Table 1**, demographic and diabetes characteristics of the analysis population are presented stratified by the 4 subgroups defined in **Figure 2**.

Table 1: Demographic and diabetes characteristics of the study population.

Characteristics		Sequential enrollment cohort		Enrichment permitted cohort	
		Primary care N=45 subjects	Ophthalmology N=190 subjects	Primary care N=335 subjects	Ophthalmology N=85 subjects
Age in years	**mean (Std. Dev)**	51.9 (10.0)	60.5 (11.0)	51.5 (16.1)	60.0 (10.3)
	median	52	61.5	54	60
	range	27.0 - 75.0	27.0 - 88.0	22.0 - 86.0	33.0 - 83.0
HbA1c	**mean (Std. Dev)**	9.2 (2.2)	7.0 (1.5)	7.8 (1.7)	7.5 (1.6)
	median	9.1	6.8	7.5	7.2
	range	6.1 - 13.1	5.0 - 14.0	5.1 - 15.3	5.7 - 13.0
Diabetes duration in years	**mean (Std. Dev)**	7.9 (7.6)	11.3 (10.4)	14.4 (10.9)	15.7 (8.9)
	median	5	8	13	13
	range	0.0 - 34.0	0.0 - 50.0	0.0 - 51.0	0.0 - 48.0
Female % (count)		44.4% (20)	61.6% (117)	44.5% (149)	70.6% (60)
Race % (count)	**American Indian or Alaska Native**	0.0% (0)	0.0% (0)	0.3% (1)	2.4% (2)
	Asian	8.9% (4)	2.6% (5)	1.2% (4)	0.0% (0)
	Black or African-American	4.4% (2)	20.0% (38)	14.9% (50)	14.1% (12)
	Native Hawaiian or Pacific Islander	0.0% (0)	0.5% (1)	0.0% (0)	0.0% (0)
	Other	0.0% (0)	6.3% (12)	1.5% (5)	8.2% (7)
	White	86.7% (39)	70.5% (134)	82.1% (275)	75.3% (64)
Ethnicity % (count)	**Non-Hispanic/Latino**	17.8% (8)	80.0% (152)	86.6% (290)	78.8% (67)
	Hispanic/Latino	82.2% (37)	20.0% (38)	13.4% (45)	21.2% (18)
Diabetes type % (count)	**Type 1**	13.3% (6)	3.7% (7)	36.7% (123)	3.5% (3)
	Type 2	86.7% (39)	96.3% (183)	63.3% (212)	96.5% (82)

4. Summary of Clinical Study Results

The primary outcomes were the sensitivity and specificity of EyeArt for detecting mtmDR and vtDR in subject eyes. The performance measures are separately reported for each cohort.

a) EyeArt performance for detecting more than mild DR (mtmDR) and vision-threatening DR (vtDR) in the sequentially enrolled cohort

In **Table 2**, the key performance measures are summarized for the sequentially enrolled cohorts at primary care and ophthalmology sites. Contingency tables and additional performance measures for sequential enrollment cohorts at primary care sites and ophthalmology sites are

presented in the Appendix in **Table 6** and **Table 7** for EyeArt mtmDR and vtDR outputs respectively.

Table 2: Summary of EyeArt performance for sequentially enrolled cohorts at primary care and ophthalmology sites.

	Sequentially enrolled cohort			
	EyeArt mtmDR output		EyeArt vtDR output	
	Primary care (N=90 eyes)	Ophthalmology (N=380 eyes)	Primary care (N=90 eyes)	Ophthalmology (N=380 eyes)
Sensitivity	100.0% [74.1% - 100%]† (11/11)	94.9% [86.4% - 100.0%] (37/39)	100.0% [51.0% - 100%]† (4/4)	88.9% NA (8/9)
Specificity	92.0% [85.1% - 97.5%] (69/75)	86.7% [82.1% - 90.7%] (281/324)	97.5% [93.4% - 100.0%] (77/79)	93.8% [90.4% - 96.6%] (331/353)
Imageability	96.6% [90.9% - 100.0%] (86/89)	98.6% [97.0% - 99.7%] (363/368)	96.5% [90.6% - 100.0%] (83/86)	98.6% [97.0% - 99.7%] (362/367)
Positive predictive value (PPV)	64.7% [40.0% - 85.7%] (11/17)	46.2% [32.2% - 59.0%] (37/80)	66.7% NA (4/6)	26.7% [11.1% - 44.4%] (8/30)
Negative predictive value (NPV)	100.0% [94.7% - 100%]† (69/69)	99.3% [98.2% - 100.0%] (281/283)	100.0% [95.2% - 100%]† (77/77)	99.7% [99.1% - 100.0%] (331/332)
Disease prevalence	12.2% [4.4% - 20.0%] (11/90)	10.5% [6.6% - 15.0%] (40/380)	4.4% [0.0% - 11.1%] (4/90)	2.4% [1.0% - 4.2%] (9/380)

All the 95% confidence intervals (CIs) are computed using the clustered bootstrap method that takes into consideration the correlation between eyes of the same subject. "NA" indicates instances when this CI method fails due to small sample sizes.

†For cases with proportion of 100%, the 95% confidence intervals using clustered bootstrap are [100% - 100%], hence the Wilson method is used, which however is not designed to consider eye correlation.

b) EyeArt performance for detecting more than mild DR (mtmDR) and vision-threatening DR (vtDR) in the enrichment-permitted cohort

In**Table** , the key performance measures are summarized for the enrichment-permitted cohorts at primary care and ophthalmology sites. Contingency tables and additional performance measures for enrichment-permitted cohorts at primary care sites and ophthalmology sites are presented in the Appendix in **Table 8** and **Table 9** respectively.

Table 3: Summary of EyeArt performance at primary care and ophthalmology cohorts when enrichment was permitted.

	Enrichment-permitted cohort			
	EyeArt mtmDR output		EyeArt vtDR output	
	Primary care (N=670 eyes)	Ophthalmology (N=170 eyes)	Primary care (N=670 eyes)	Ophthalmology (N=170 eyes)
Sensitivity	92.9% [87.1% - 97.5%] (92/99)	96.6% [87.5% - 100.0%] (28/29)	91.7% [80.0% - 100.0%] (22/24)	100.0% [51.0% - 100%]† (4/4)
Specificity	85.6% [82.2% - 89.1%] (457/534)	85.2% [78.1% - 91.5%] (115/135)	92.2% [89.6% - 94.6%] (553/600)	89.8% [83.9% - 95.4%] (141/157)
Imageability	96.8% [94.8% - 98.5%] (633/654)	96.5% [91.8% - 100.0%] (164/170)	96.7% [94.8% - 98.5%] (624/645)	97.0% [92.9% - 100.0%] (161/166)
Positive predictive value (PPV)	54.4% [45.3% - 63.6%] (92/169)	58.3% [40.3% - 74.5%] (28/48)	31.9% [19.7% - 44.4%] (22/69)	20.0% [0.0% - 42.1%] (4/20)
Negative predictive value (NPV)	98.5% [97.3% - 99.5%] (457/464)	99.1% [97.2% - 100.0%] (115/116)	99.6% [99.1% - 100.0%] (553/555)	100.0% [97.3% - 100%]† (141/141)
Disease prevalence	15.5% [12.1% - 19.3%] (104/670)	19.4% [11.8% - 27.6%] (33/170)	4.2% [2.4% - 6.3%] (28/670)	2.4% [0.0% - 5.9%] (4/170)

All the 95% confidence intervals (CIs) are computed using the clustered bootstrap method that takes into consideration the correlation between eyes of the same subject. "NA" indicates instances when this CI method fails due to small sample sizes.

†For cases with proportion of 100%, the 95% confidence intervals using clustered bootstrap are [100% - 100%], hence the Wilson method is used, which however is not designed to consider eye correlation.

c) Imageability

EyeArt disease results (*positive* or *negative*) were obtained for a vast majority of eyes (*imageability* of 96.5% or greater) that received a completed FPRC grading.

- Sequential enrollment cohort at primary care sites had an imageability of 96.5% or greater, where gradable results were obtained in the first attempt without dilation in (81/86) 94.2% eyes.
- Sequential enrollment cohort at ophthalmology sites had an imageability of 98.6%, where gradable results were obtained in the first attempt without dilation in (300/367) 81.7% eyes.
- Enrichment-permitted cohort at primary care sites had an imageability of 96.7% or greater, where gradable results were obtained in the first attempt without dilation in (582/654) 89.0% eyes.

- Enrichment-permitted cohort at ophthalmology sites had an imageability of 96.5% or greater, where gradable results were obtained in the first attempt without dilation in (142/170) 83.5% eyes.

5. Precision Study

Eyenuk conducted a separate precision (repeatability and reproducibility) study on 62 subjects at 2 US primary care sites (31 subjects each) that evaluated the EyeArt results when retinal photography was repeated using the Canon CR-2 AF camera with different operator-camera pairs. Repeatability (intra-operator variability) and reproducibility (inter-operator variability) were specifically analyzed using data from Cohorts P1 and P2 from the study as described in the following sections. All the 95% CIs reported here are computed using the clustered bootstrap method taking into consideration the correlation between eyes.

a) Repeatability (Intra-operator variability) analysis

For subjects at the first site, Cohort P1, there were 3 operator-camera pairings consisting of 3 different operators using 2 different camera units of the same model (each operator operated a given camera unit). Each eye of each subject was to undergo imaging by each operator-camera pair twice for a total of 186 pairs of images (where one "image" = a disc-centered image and a macula-centered image for one eye). The order of camera and operator pairings was randomized. Data for 6 eyes of 3 subjects were missing, because the first images of each eye were not obtained according to the protocol (dilate and repeat imaging, if the initial result was ungradable). For subjects at the second site, Cohort P2, each eye of each subject was to undergo imaging 3 times by a single operator using a single camera.

The observed intra-operator overall agreement (OA) for Cohort P1 was 93.9% [95% CI: 89.7% - 97.7%] for the EyeArt mtmDR output and 98.9% [95% CI: 96.5% - 100.0%] for the EyeArt vtDR output. The observed intra-operator OA for Cohort P2 was 93.5% [95% CI: 87.1% - 98.4%] for the EyeArt mtmDR output and 96.8% [95% CI: 91.9% - 100.0%] for the EyeArt vtDR output. Contingency tables and additional performance measures are reported in **Table 10 - Table 12** in the Appendix.

b) Reproducibility (Inter-operator variability) analysis

The reproducibility was measured in Cohort P1 by analyzing the agreement among the EyeArt results for each eye from the first of two Canon CR-2 AF images obtained by each of the 3 operators. Because the first images of 6 eyes of 3 subjects were missing due to protocol deviations, these were replaced with the second image in each case. For the EyeArt mtmDR output, an inter-operator OA of 90.3% [95% CI: 82.3% - 96.8%] was achieved and for the EyeArt vtDR output, an inter-operator OA of 96.8% [95% CI: 90.3% - 100.0%] was achieved. Contingency tables and additional performance measures are reported in the Appendix in **Table 13** for the mtmDR output and in **Table 14** for the vtDR output.

6. Human Factors Validation Testing

The human factors data support the safety and effectiveness of the camera operation and use of the EyeArt Client user interface. The human factors report contained information from a formative study and a validation study using EyeArt v2.1.0 rev005. A review of detailed human factors engineering processes, including use-related risk impact assessment of the device modification referred to as EyeArt v2.1.0 rev006, indicated that no new critical tasks were introduced or existing critical tasks in v2.1.0 rev005 were impacted by the device modification. The formative study was conducted to confirm the data in the task analysis and risk assessment and to uncover any additional potential use errors. The critical task for using EyeArt is the ability to capture four images of sufficient quality to produce EyeArt gradable results. The results of the simulated-use human factors validation study for using EyeArt with the Canon CR-2 AF camera indicate that camera operators with no prior retinal photography experience can be trained to capture four medical-grade retinal images from a vast majority of subjects.

E. Substantial Equivalence

EyeArt has the same intended use and similar indications for use (IFU) as the predicate IDx-DR device. **Table 4** provides a comparison between the IFU of EyeArt and that of the predicate device. The differences in the IFU do not alter the intended use.

Table 4: Comparison of indications for use of the EyeArt device and the predicate device

EyeArt (subject device, K200667)	Predicate Device (IDx-DR DEN180001)	Discussion
EyeArt is indicated for use by healthcare providers to automatically detect more than mild diabetic retinopathy and vision-threatening diabetic retinopathy (severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy and/or diabetic macular edema)	*IDx-DR is intended for use by health care providers to automatically detect more than mild diabetic retinopathy (mtmDR)*	Substantially equivalent
in eyes of adults diagnosed with diabetes who have not been previously diagnosed with more than mild diabetic retinopathy.	*in adults diagnosed with diabetes who have not been previously diagnosed with diabetic retinopathy.*	
EyeArt is indicated for use with Canon CR-2 AF and Canon CR-2 Plus AF cameras in both primary care and eye care settings.	*IDx-DR is indicated for use with the Topcon NW400.*	

As summarized in **Table 5**, the subject and predicate devices have similar technological characteristics. Although the specific algorithms differ, these differences do not raise new issues of safety and effectiveness as compared to the predicate and are supported by the clinical performance data.

Table 5: Comparison of the technological elements of the EyeArt device and the predicate device.

	EyeArt (subject device, K200667)	**Predicate device (IDx-DR, DEN180001)**	**Discussion**
Technological principle	Artificial Intelligence software as a medical device	Artificial Intelligence software as a medical device	Equivalent
Inputs	Macula and disc centered color fundus images with 45° field of view, 2 per eye	Macula and disc centered color fundus images with 45° field of view, 2 per eye	Equivalent
Outputs	For each eye: **More than mild diabetic retinopathy (mtmDR):** one of *negative for mtmDR, mtmDR detected,* or *ungradable*. **Vision-threatening diabetic retinopathy (vtDR):** one of *negative for vtDR, vtDR detected,* or *ungradable*.	For the patient: **More than mild diabetic retinopathy (mtmDR):** one of *mtmDR not detected, mtmDR detected,* or *insufficient quality*	Equivalent mtmDR outputs, since this refers to the International Clinical Diabetic Retinopathy (ICDR) and Diabetic Macular Edema Disease Severity Scales' definitions of moderate non-proliferative diabetic retinopathy or worst and/or the presence of diabetic macular edema (DME). EyeArt eye-level output (rather than patient-level output by the predicate) does not alter intended use and is supported by clinical performance data. Additional vision-threatening DR detection does not alter intended use and is supported by clinical performance data.
Architecture	Client software (user facing) transfers images to and receives results from Analysis Computation Engine through Server.	Client software (user facing) transfers images to and receives results from Analysis through Web Server.	Equivalent
Indicated Cameras	Canon CR-2 AF and Canon CR-2 Plus AF	Topcon NW400 camera	The legally marketed cameras specified for use are being used to capture macula and disc centered retinal images with 45° field of view (2 per eye) for both EyeArt and predicate device. The clinical performance data support the use of EyeArt with the indicated cameras.

F. Conclusions

EyeArt is substantially equivalent to the predicate device, IDx-DR. EyeArt has the same intended use and equivalent indications for use. The technological characteristics are similar. The technological differences between EyeArt and its predicate device raise no new issues of safety or effectiveness. Performance data support the substantial equivalence of EyeArt to the predicate device.

G. Appendix

1. Detailed results from the EyeArt pivotal study

In this section we present detailed results from the pivotal study. We present contingency tables along with other quantities for the following cohorts: (1) sequentially enrolled cohort at primary care sites (mtmDR - **Table 6**; vtDR - **Table 7**), (2) sequentially enrolled cohort at ophthalmology sites (mtmDR - **Table 6**; vtDR - **Table 7**), (3) enrichment-permitted cohort at primary care sites (mtmDR - **Table 8**; vtDR - **Table 9**), and (4) enrichment-permitted cohort at ophthalmology sites (mtmDR - **Table 8**; vtDR - **Table 9**). The parameters that are presented in **Table 6** to **Table 9** are defined below:

	Reading center reference standard			
	Positive	**Negative**	**Ungradable**	**Total**
EyeArt Positive	PP	PN	PU	DP=PP+PN+PU
EyeArt Negative	NP	NN	NU	DN=NP+NN+NU
EyeArt Ungradable	UP	UN	UU	DU=UP+UN+UU
Total	TP = PP+NP+UP	TN = PN+NN+UN	TU=PU+NU+UN	N=TP+TN+TU

Sensitivity: PP/(PP+NP)

Specificity: NN/(NN+PN)

Imageability: (PP+NN+PN+NP)/(TP+TN)

Positive predictive value (PPV): PP/(PP+PN)

Negative predictive value (NPV): NN/(NN+NP)

Positive likelihood ratio: (PP/TP)/(PN/TN)

Negative likelihood ratio: (NP/TP)/(NN/TN)

Sensitivity considering ungradables: PP/(PP+NP+UP)

Specificity considering ungradables: NN/(PN+NN+UN)

PPV considering ungradables: PP/(PP+PN+PU)

NPV considering ungradables: NN/(NN+NP+NU)

Disease prevalence: TP/N, Percentage of eyes identified as positive per reference standard.

Table 6: EyeArt eye-level mtmDR analysis for subjects enrolled during sequential enrollment.

Sequential enrollment cohort mtmDR	Primary care (45 subjects, 90 eyes)				Ophthalmology (190 subjects, 380 eyes)			
	mtmDR Reading center reference standard				mtmDR Reading center reference standard			
	Pos	**Neg**	**Ung**	**Tot**	**Pos**	**Neg**	**Ung**	**Tot**
EyeArt Positive	11	6	0	17	37	43	1	81
EyeArt Negative	0	69	0	69	2	281	8	291
EyeArt Ungradable	0	3	1	4	1	4	3	8
Total	11	78	1	90	40	328	12	380
Sensitivity	100.0% [74.1% - 100%]† (11/11)				94.9% [86.4% - 100.0%] (37/39)			
Specificity	92.0% [85.1% - 97.5%] (69/75)				86.7% [82.1% - 90.7%] (281/324)			
Imageability	96.6% [90.9% - 100.0%] (86/89)				98.6% [97.0% - 99.7%] (363/368)			
Positive Predictive Value (PPV)	64.7% [40.0% - 85.7%] (11/17)				46.2% [32.2% - 59.0%] (37/80)			
Negative Predictive Value (NPV)	100.0% [94.7% - 100%]† (69/69)				99.3% [98.2% - 100.0%] (281/283)			
Positive Likelihood Ratio	13 [7.000 - 41.012]				7.056 [5.118 - 10.184]			
Negative Likelihood Ratio	0 [0.0 – 0.0]				0.058 [0.000 - 0.155]			
Sensitivity considering ungradables	100% [74.1% - 100%]† (11/11)				92.5% [82.6% - 100.0%] (37/40)			
Specificity considering ungradables	88.5% [80.0% - 95.8%] (69/78)				85.7% [80.9% - 89.7%] (281/328)			
PPV considering ungradables	64.7% [40.0% - 85.7%] (11/17)				45.7% [31.8% - 58.3%] (37/81)			
NPV considering ungradables	100.0% [94.7% - 100.0%]† (69/69)				96.6% [94.1% - 98.6%] (281/291)			
Disease (mtmDR) prevalence in this population	12.2% [4.4% - 20.0%] (11/90)				10.5% [6.6% - 15.0%] (40/380)			

All the 95% confidence intervals (CIs) are computed using the clustered bootstrap method that takes into consideration the correlation between eyes of the same subject. "NA" indicates instances when this CI method fails due to small sample sizes.
†For cases with proportion of 100%, the 95% confidence intervals using clustered bootstrap are [100% - 100%], hence the Wilson method is used, which however is not designed to consider eye correlation.

Table 7: EyeArt eye-level vtDR analysis for subjects enrolled during sequential enrollment.

Sequential enrollment cohort	Primary care (45 subjects, 90 eyes)				Ophthalmology (190 subjects, 380 eyes)			
vtDR	vtDR Reading center reference standard				vtDR Reading center reference standard			
	Pos	Neg	Ung	Tot	Pos	Neg	Ung	Tot
EyeArt Positive	4	2	3	9	8	22	1	31
EyeArt Negative	0	77	0	77	1	331	9	341
EyeArt Ungradable	0	3	1	4	0	5	3	8
Total	4	82	4	90	9	358	13	380
Sensitivity	100.0% [51.0% - 100%]† (4/4)				88.9% NA (8/9)			
Specificity	97.5% [93.4% - 100.0%] (77/79)				93.8% [90.4% - 96.6%] (331/353)			
Imageability	96.5% [90.6% - 100.0%] (83/86)				98.6% [97.0% - 99.7%] (362/367)			
Positive Predictive Value (PPV)	66.7% NA (4/6)				26.7% [11.1% - 44.4%] (8/30)			
Negative Predictive Value (NPV)	100.0% [95.2% - 100%]† (77/77)				99.7% [99.1% - 100.0%] (331/332)			
Positive Likelihood Ratio	41.0 NA				14.465 [8.595 - 27.426]			
Negative Likelihood Ratio	0.0 [0.000 - 0.000]				0.12 [0.000 - 0.426]			
Sensitivity considering ungradables	100.0% [51.0% - 100%]† (4/4)				88.9% [60.0% - 100.0%] (8/9)			
Specificity considering ungradables	93.9% [86.5% - 98.8%] (77/82)				92.5% [88.7% - 95.6%] (331/358)			
PPV considering ungradables	44.4% NA (4/9)				25.8% [10.8% - 42.3%] (8/31)			
NPV considering ungradables	100.0% [95.2% - 100.0%]† (77/77)				97.1% [95.0% - 98.8%] (331/341)			
Disease (vtDR) prevalence in this population	4.4% [0.0% - 11.1%] (4/90)				2.4% [1.0% - 4.2%] (9/380)			

All the 95% confidence intervals (CIs) are computed using the clustered bootstrap method that takes into consideration the correlation between eyes of the same subject. "NA" indicates instances when this CI method fails due to small sample sizes.
†For cases with proportion of 100%, the 95% confidence intervals using clustered bootstrap are [100% - 100%], hence the Wilson method is used, which however is not designed to consider eye correlation.

Table 8: EyeArt eye-level mtmDR analysis for subjects enrolled when enrichment was permitted.

Enrichment-permitted cohort mtmDR	Primary care (335 subjects, 670 eyes)				Ophthalmology (85 subjects, 170 eyes)			
	mtmDR Reading center reference standard				mtmDR Reading center reference standard			
	Pos	Neg	Ung	Tot	Pos	Neg	Ung	Tot
EyeArt Positive	92	77	2	171	28	20	0	48
EyeArt Negative	7	457	9	473	1	115	0	116
EyeArt Ungradable	5	16	5	26	4	2	0	6
Total	104	550	16	670	33	137	0	170
Sensitivity	92.9% [87.1% - 97.5%] (92/99)				96.6% [87.5% - 100.0%] (28/29)			
Specificity	85.6% [82.2% - 89.1%] (457/534)				85.2% [78.1% - 91.5%] (115/135)			
Imageability	96.8% [94.8% - 98.5%] (633/654)				96.5% [91.8% - 100.0%] (164/170)			
Positive Predictive Value (PPV)	54.4% [45.3% - 63.6%] (92/169)				58.3% [40.3% - 74.5%] (28/48)			
Negative Predictive Value (NPV)	98.5% [97.3% - 99.5%] (457/464)				99.1% [97.2% - 100.0%] (115/116)			
Positive Likelihood Ratio	6.319 [4.988 - 8.473]				5.812 [3.736 - 10.182]			
Negative Likelihood Ratio	0.081 [0.029 - 0.145]				0.036 [0.000 - 0.131]			
Sensitivity considering ungradables	88.5% [80.5% - 94.9%] (92/104)				84.9% [65.5% - 100.0%] (28/33)			
Specificity considering ungradables	83.1% [79.4% - 86.8%] (457/550)				83.9% [76.6% - 90.6%] (115/137)			
PPV considering ungradables	53.8% [44.6% - 63.1%] (92/171)				58.3% [40.3% - 74.5%] (28/48)			
NPV considering ungradables	96.6% [94.5% - 98.4%] (457/473)				99.1% [97.2% - 100.0%] (115/116)			
Disease (mtmDR) prevalence in this population	15.5% [12.1% - 19.3%] (104/670)				19.4% [11.8% - 27.6%] (33/170)			

All the 95% confidence intervals (CIs) are computed using the clustered bootstrap method that takes into consideration the correlation between eyes of the same subject. “NA” indicates instances when this CI method fails due to small sample sizes.

Table 9: EyeArt eye-level vtDR analysis for subjects enrolled when enrichment was allowed.

Enrichment permitted cohort vtDR	Primary care (335 subjects, 670 eyes)				Ophthalmology (85 subjects, 170 eyes)			
	vtDR Reading center reference standard				vtDR Reading center reference standard			
	Pos	Neg	Ung	Tot	Pos	Neg	Ung	Tot
EyeArt Positive	22	47	9	78	4	16	1	21
EyeArt Negative	2	553	11	566	0	141	2	143
EyeArt Ungradable	4	17	5	26	0	5	1	6
Total	28	617	25	670	4	162	4	170
Sensitivity	91.7% [80.0% - 100.0%] (22/24)				100.0% [51.0% - 100%]† (4/4)			
Specificity	92.2% [89.6% - 94.6%] (553/600)				89.8% [83.9% - 95.4%] (141/157)			
Imageability	96.7% [94.8% - 98.5%] (624/645)				97.0% [92.9% - 100.0%] (161/166)			
Positive Predictive Value (PPV)	31.9% [19.7% - 44.4%] (22/69)				20.0% [0.0% - 42.1%] (4/20)			
Negative Predictive Value (NPV)	99.6% [99.1% - 100.0%] (553/555)				100.0% [97.3% - 100%]† (141/141)			
Positive Likelihood Ratio	10.315 [6.965 - 15.704]				10.125 [6.403 - 22.571]			
Negative Likelihood Ratio	0.08 [0.000 - 0.195]				0 [0.0 - 0.0]			
Sensitivity considering ungradables	78.6% [58.8% - 95.8%] (22/28)				100.0% [51.0% - 100%]† (4/4)			
Specificity considering ungradables	89.6% [86.6% - 92.4%] (553/617)				87.0% [80.1% - 93.1%] (141/162)			
PPV considering ungradables	28.2% [17.4% - 38.9%] (22/78)				19.0% [0.0% - 38.5%] (4/21)			
NPV considering ungradables	97.7% [96.0% - 99.1%] (553/566)				98.6% [95.7% - 100.0%] (141/143)			
Disease (vtDR) prevalence in this population	4.2% [2.4% - 6.3%] (28/670)				2.4% [0.0% - 5.9%] (4/170)			

All the 95% confidence intervals (CIs) are computed using the clustered bootstrap method that takes into consideration the correlation between eyes of the same subject. "NA" indicates instances when this CI method fails due to small sample sizes.
†For cases with proportion of 100%, the 95% confidence intervals using clustered bootstrap are [100% - 100%], hence the Wilson method is used, which however is not designed to consider eye correlation.

2. Detailed results from the EyeArt precision study

In this section, we present detailed results of the EyeArt precision study including contingency tables and the following parameters, defined below.

For 3x3 contingency tables, the definitions are as follows:

EyeArt result 2 / EyeArt result 1	**EyeArt Negative**	**EyeArt Positive**	**EyeArt Ungradable**	**Total**
EyeArt Negative	NN	NP	NU	NT=NN+NP+NU
EyeArt Positive	PN	PP	PU	PT=PN+PP+PU
EyeArt Ungradable	UN	UP	UU	UT=UN+UP+UU
Total	TN = NN+PN+UN	TP = NP+PP+UP	TU=NU+PU+UN	N=TN+TP+TU

Overall agreement (OA): (PP+NN+UU) / N

Average Positive Agreement (APA): (2*PP) / (TP + PT)

Average Negative Agreement (ANA): (2*NN) / (TN + NT)

Average Ungradable Agreement (AUA): (2*UU) / (TU + UT)

For 3-dimensional (3x3x3) contingency tables, the definitions are as follows:

Overall agreement (OA) for the 3x3x3 contingency tables is computed as follows, where x_{ij} is the count of triplets of operations with outcomes (i, j, k) where each outcome is one of n (negative), p (positive), and u (ungradable):

$$OA = \left(x_{nnn} + x_{ppp} + x_{uuu}\right) / \left(\sum_{i,j,k=n,p,u} x_{ijk} \right)$$

The percent agreements for the 3x3x3 contingency tables are evaluated as follows, where R_1, R_2, and R_3 stand for EyeArt output for the three operations 1, 2, and 3 respectively that are used to build the 3x3x3 contingency table:

Average positive agreement (APA) is computed as:

$$APA = \frac{\sum_{1 \le i < j \le 3} 2P(R_i = 1 \cap R_j = 1)}{2 \sum_{1 \le i \le 3} P(R_i = 1)}$$

Average negative agreement (ANA) is computed as:

$$ANA = \frac{\sum_{1 \le i < j \le 3} 2P(R_i = 0 \cap R_j = 0)}{2 \sum_{1 \le i \le 3} P(R_i = 0)}$$

Average ungradable agreement (AUA) is computed as:

$$AUA = \frac{\sum_{1 \le i < j \le 3} 2P(R_i = Ungradable \cap R_j = Ungradable)}{2 \sum_{1 \le i \le 3} P(R_i = Ungradable)}$$

a. Intra-operator repeatability

Table 10 presents the intra-operator repeatability for the EyeArt mtmDR and vtDR outputs, combined across all three operator-camera pairings from Cohort P1, and the 3x3 contingency tables. For this Cohort P1, 3 operators were to each provide one intra-operator pair per eye for a total of 186 eye pairs (3 intra-operator pairs x 31 subjects x 2 eyes/subject). There were 6 missing pairs due to protocol deviations, leaving 180 pairs that were performed per protocol.

Table 10: EyeArt mtmDR and vtDR repeatability (intra-operator) with Canon CR-2 AF across all 3 operator-camera pairings for Cohort P1.

Cohort P1 repeatability	**mtmDR**			**vtDR**		
Repeat 2 / Repeat 1	Negative	Positive	Ungradable	Negative	Positive	Ungradable
Negative	109	6	0	151	0	0
Positive	3	56	0	0	23	0
Ungradable	1	1	4	2	0	4
OA	93.9% [89.7% - 97.7%] (169/180)			98.9% [96.5% - 100.0%] (178/180)		
APA	91.8% [86.1% - 97.0%]			100.0% [92.3% - 100.0%]		
ANA	95.6% [92.5% - 98.3%]			99.3% [97.9% - 100.0%]		
AUA	80.0% [49.0% - 94.3%]			80.0% [49.0% - 94.3%]		
OA* (protocol deviations considered ungradable)	90.9% [84.7% - 95.7%] (169/186)			95.7% [91.4% - 98.9%] (178/186)		

For Cohort P2, the intra-operator repeatability for the EyeArt mtmDR and vtDR outputs is presented in **Table 11** and **Table 12** respectively, and the 3-dimensional (3x3x3) contingency tables corresponding to the 3 repeats (operations) per subject eye for the 31 subjects in this cohort.

Table 11: EyeArt mtmDR repeatability with Canon CR-2 AF camera for Cohort P2. For this cohort, each subject underwent 3 EyeArt operations with the same operator-camera pairing.

	Cohort P2 repeatability (mtmDR)								
	Repeat 3 result = Negative			**Repeat 3 result = Positive**			**Repeat 3 result = Ungradable**		
Repeat 2 / Repeat 1	Neg.	Pos.	Ung.	Neg.	Pos.	Ung.	Neg.	Pos.	Ung.
Negative	36	2	0	0	0	0	0	0	0
Positive	0	1	0	1	22	0	0	0	0
Ungradable	0	0	0	0	0	0	0	0	0
OA	93.5% [87.1% - 98.4%] (58/62)								
APA	94.4% [88.9% - 98.6%]								
ANA	96.5% [92.0% - 99.2%]								
AUA	Cannot be calculated since no eyes with ungradable EyeArt results								

Table 12: EyeArt vtDR repeatability with Canon CR-2 AF camera for Cohort P2. For this cohort, each subject underwent 3 EyeArt operations with the same operator-camera pairing.

	Cohort P2 repeatability (vtDR)								
	Repeat 3 result = Negative			**Repeat 3 result = Positive**			**Repeat 3 result = Ungradable**		
Repeat 2 / Repeat 1	Neg.	Pos.	Ung.	Neg.	Pos.	Ung.	Neg.	Pos.	Ung.
Negative	50	1	0	0	1	0	0	0	0
Positive	0	0	0	0	10	0	0	0	0
Ungradable	0	0	0	0	0	0	0	0	0
OA	96.8% [91.9% - 100.0%] (60/62)								
APA	93.9% [78.0% - 100.0%]								
ANA	98.7% [96.5% - 100.0%]								
AUA	Cannot be calculated since no eyes with ungradable EyeArt results								

b. Between-operator reproducibility

Table 13 and **Table 14** present the between-operator (inter-operator) reproducibility results for the EyeArt mtmDR and vtDR outputs respectively. These results are from Cohort P1, where 3 operators each conducted two operations for each subject. We use the first operation by each operator to construct and report a 3-dimensional contingency matrix (3x3x3). The three missing operations for a given subject were replaced with the next equivalent operation by the same operator-camera pairing.

Table 13: EyeArt reproducibility for mtmDR results with Canon CR-2 AF camera.

	Cohort P1 reproducibility (mtmDR)								
	Operator C3 result = Negative			**Operator C3 result = Positive**			**Operator C3 result = Ungradable**		
Op C2 / Op C1	Neg.	Pos.	Ung.	Neg.	Pos.	Ung.	Neg.	Pos.	Ung.
Negative	37	1	0	1	0	0	0	0	0
Positive	0	1	0	1	19	0	0	0	0
Ungradable	0	0	0	0	0	0	1	1	0
OA	90.3% [82.3% - 96.8%] (56/62)								
APA	92.2% [81.4% - 98.3%]								
ANA	95.8% [91.9% - 99.1%]								
AUA	50.0% [21.5% - 78.5%]								

Table 14: EyeArt reproducibility for vtDR results with Canon CR-2 AF camera.

	Cohort P1 reproducibility (vtDR)								
	Operator C3 result = Negative			**Operator C3 result = Positive**			**Operator C3 result = Ungradable**		
Op C2 / Op C1	Neg.	Pos.	Ung.	Neg.	Pos.	Ung.	Neg.	Pos.	Ung.
Negative	51	0	0	0	0	0	0	0	0
Positive	0	0	0	0	9	0	0	0	0
Ungradable	0	0	0	0	0	0	2	0	0
OA	96.8% [90.3% - 100.0%] (60/62)								
APA	100.0% [93.4% - 100.0%]†								
ANA	98.7% [95.3% - 100.0%]								
AUA	50.0% [21.5% - 78.5%]								

†For cases with proportion of 100%, the 95% confidence intervals using clustered bootstrap are [100% - 100%], hence the Wilson method is used, which however is not designed to consider eye correlation.