

STUDY PROTOCOL

Version: 1.4

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Site: Retina of North Texas

1. Study Title

Prospective Evaluation of Retinal Imaging and Clinical Data for Prediction of Ocular and Systemic Disease

2. Background and Rationale

The retina is a highly vascularized and metabolically active neural tissue that reflects systemic microvascular and neurologic health. Retinal imaging has long been used clinically to assess conditions such as hypertension, diabetes, vascular disease, and common ocular disorders. Recent large-scale studies have demonstrated associations between retinal structural features, including retinal layer thickness and microvascular characteristics, and systemic conditions such as cardiovascular disease, stroke, neurodegenerative disorders, and overall mortality risk (1,2,5).

In parallel, advances in artificial intelligence and deep learning have enabled automated extraction of clinically meaningful features from retinal images, with strong performance in detection of diabetic retinopathy and broader ophthalmic image analysis (3,4). These technologies create an opportunity to develop scalable, non-invasive biomarkers for both ocular and systemic disease.

Despite these advances, much of the published work has relied on retrospective datasets. There remains a need for prospective, real-world data collection linking retinal imaging with clinical information to support robust model development and validation. This study is designed to address that gap using retinal images obtained during routine care together with associated clinical data.

3. Study Objectives

3.1 Primary Objective

- Develop machine learning models to predict cardiovascular and neurologic disease risk from multimodal retinal imaging and associated clinical data.

3.2 Secondary Objectives

- Develop machine learning models to detect ocular diseases including macular degeneration, glaucoma, and diabetic retinopathy.
- Evaluate associations between retinal imaging features and systemic and ocular disease.
- Assess feasibility of prospective collection of high-quality retinal imaging and linked clinical data for future biomarker development.

4. Study Design

This is a prospective, observational, minimal-risk study. No investigational treatment will be administered, and participation in the study will not alter clinical care, diagnosis, treatment, or follow-up recommendations.

5. Study Population

5.1 Inclusion Criteria

- Adults aged 18 years and older.
- Able to provide informed consent in English.
- Undergoing retinal imaging as part of routine clinical care.

5.2 Exclusion Criteria

- Unable to provide informed consent.
- Retinal image quality insufficient for analysis.
- Any circumstance in which the investigator determines study participation is not appropriate.

6. Target Enrollment and Sample Size Justification

Up to 5,000 subjects will be enrolled. This sample size is intended to provide sufficient retinal imaging and linked clinical data for machine learning model development, training, validation, and testing, while accounting for incomplete datasets, poor image quality, withdrawals, and variability in disease prevalence. A large data set is necessary to refine machine learning algorithms.

7. Recruitment and Enrollment Workflow

Potential participants will be identified during routine clinical care. Eligible adults may be approached by study personnel, including clinical staff or research coordinators, either prior to or following their clinical evaluation. Participants will be approached in a private and appropriate setting, and sufficient time will be provided to review the consent form and ask questions. Enrollment will occur only after informed consent and HIPAA authorization have been obtained. Relevant clinical data may be included in the study dataset and obtained from the participant's healthcare providers. Participation in the study will not affect clinical care, and individuals may decline participation without impact on their treatment or relationship with their provider. No recruitment advertisements, diaries, study cards, or retention materials are required for this protocol at the time of submission.

8. Study Procedures

Participants will undergo retinal imaging, including non-invasive fundus photography and optical coherence tomography (OCT), with or without OCT angiography, as part of routine clinical care. Clinical data may also be collected from the medical record, including demographics, medical history, diagnoses, medications, vital signs, and laboratory data if available. The participants healthcare providers may be contacted to obtain this data.

No subject will be asked to undergo retinal imaging solely for research purposes. All imaging utilized in this study will be obtained as part of routine clinical care, and participation in the study will not result in any additional procedures or changes to clinical management.

Data collection will occur prospectively at the time of routine clinical encounters. In addition, clinical data may be abstracted from the medical record either as a one-time extraction or longitudinally over time to capture relevant outcomes and disease progression, when available. No additional study visits or procedures will be required.

9. Artificial Intelligence System Description and Regulatory Framework

The investigational system is a machine learning–based clinical decision support tool designed to analyze retinal imaging data, including fundus photography, optical coherence tomography (OCT), and OCT angiography, in conjunction with structured clinical data such as demographics, medical history, vital signs, and laboratory values. The system is intended to generate probabilistic risk estimates for ocular and systemic diseases and is investigational in nature. The system will not be used to guide real-time clinical decision-making, diagnosis, or treatment and will not alter standard clinical care. Analyses will be retrospective in the sense that model development and evaluation will occur after acquisition of the clinical data and imaging.

The model architecture is based on deep learning methodologies, including convolutional neural networks (CNNs) for automated feature extraction from retinal images. These models are capable of learning hierarchical image representations without manual feature engineering. Imaging-derived features are integrated with structured clinical variables using multimodal data fusion techniques, and a prediction layer generates probabilistic outputs representing estimated disease risk. Model development follows a supervised learning approach using datasets consisting of retinal images paired with clinical outcomes derived from physician diagnoses, medical records, and laboratory data. Model performance is evaluated using standard statistical metrics, including area under the receiver operating characteristic curve, sensitivity, and specificity, and will be further assessed through prospective validation as data are collected.

Consistent with FDA draft guidance on artificial intelligence and machine learning-enabled Software as a Medical Device (SaMD), the system is being developed within a controlled lifecycle framework. This includes predefined processes for data curation, model training, validation, and performance monitoring. Model versioning and updates will be managed under a structured change control process, and updated models will not be deployed for clinical use without appropriate validation and, if applicable, regulatory review. The current study does not involve deployment of the model in a clinical setting and does not evaluate clinical performance for regulatory clearance.

The system is designed to function with **human oversight (human-in-the-loop)**, such that all clinical interpretation and decision-making remain under the authority of licensed eyecare professionals and physicians. Outputs from the system are intended to be interpretable probabilistic risk scores rather than

deterministic diagnostic conclusions. The system does not provide autonomous diagnosis, does not initiate treatment recommendations, and does not replace clinician judgment.

From a regulatory perspective, the investigational system is being developed as a potential Software as a Medical Device (SaMD) and may be subject to future FDA regulatory pathways, including 510(k) clearance or De Novo classification. However, within the context of this study, the system is used solely for research purposes and retrospective or prospective analysis of collected data. As such, the system does not currently function as a clinical diagnostic device and does not introduce additional risk to participants.

Overall, the use of the AI system in this study is limited to research, model development, and hypothesis generation. The system does not influence patient care, and its outputs are not communicated directly to patients. This design ensures that the study remains minimal risk while enabling the development and validation of predictive models aligned with FDA expectations for future clinical translation.

The data collected in this study may be used to support future regulatory submissions to the U.S. Food and Drug Administration (FDA), including but not limited to submissions related to Software as a Medical Device (SaMD) under 510(k) or De Novo pathways. Any such use will occur only after appropriate validation and in compliance with applicable regulatory requirements. The current study is not intended to establish clinical safety or effectiveness for regulatory clearance and does not involve clinical deployment of the AI system. The AI system described in this study meets the definition of Software as a Medical Device (SaMD) and is considered an investigational device; however, it is not utilized in a clinical setting and does not influence patient care.

10. Handling of Findings and Incidental Findings

Any findings, including incidental findings, will be communicated only to the treating eyecare professional and not directly to the subject by the research team. This approach is intended to ensure that any imaging-based observations are interpreted together with the full clinical picture by the eyecare professional before communication to the subject. AI-generated outputs in this study are investigational and will not be used to guide clinical care, but potential findings will be reviewed by the research team and communicated to the treating eyecare professional when warranted. These outputs will not be returned to patients. Analysis of AI outputs will occur separately from clinical workflows and solely for research and model development purposes.

11. Risks

This study presents no more than minimal risk to participants. The primary risk is potential loss of confidentiality associated with collection and storage of health information. No additional physical risk is introduced because retinal imaging used in this protocol is obtained as part of routine clinical care.

12. Potential Benefits

There is no guaranteed direct benefit to participants. Potential societal benefits include improved future detection and understanding of ocular disease and systemic disease through development of non-invasive retinal biomarkers and machine learning models.

13. Data Handling and Confidentiality

Study data will be de-identified or coded to the extent practicable and stored on secure, HIPAA-compliant systems. Access will be limited to authorized study personnel. Data may be used for research, model development, validation, and related scientific activities consistent with the informed consent and HIPAA authorization.

Study data will be coded at the time of collection, and each participant will be assigned a unique study identifier. Direct identifiers will be stored separately from study data. A linkage key connecting study identifiers to participant identity will be maintained in a secure, access-restricted environment by the Principal Investigator or designated study personnel.

To the extent practicable, datasets used for analysis and model development will be de-identified in accordance with HIPAA standards prior to use. De-identification will occur after initial data collection and quality assurance processes are completed.

All data will be stored on secure, HIPAA-compliant systems with access limited to authorized study personnel. Data may be used for research, model development, validation, and related scientific activities consistent with the informed consent and HIPAA authorization.

14. Data Retention and Destruction

Study data will be retained for a minimum of six (6) years following study completion or longer if required for regulatory, scientific, or legal purposes. De-identified datasets used for model development may be retained beyond this period to support ongoing research and validation for FDA regulatory approval.

Identifiers and linkage keys will be retained only as long as necessary to support study objectives and regulatory compliance. When no longer required, identifiable data and linkage keys will be securely destroyed using institutionally approved methods.

15. Regulatory Status

The artificial intelligence (AI) system described in this study meets the FDA definition of a medical device as Software as a Medical Device (SaMD) and is therefore considered an investigational device within the context of this research. This study qualifies for exemption from Investigational Device Exemption (IDE) requirements under 21 CFR 812.2(c)(3), as it is a **diagnostic device study** that meets the following criteria: A) The investigational device is not used as the sole basis for diagnosis or treatment decisions; B)

The investigational device does not introduce additional risk to subjects; C) The results of the investigational device are not used to guide clinical management; D) The study does not involve invasive sampling or procedures beyond routine clinical care. All data are collected as part of routine clinical care, and no invasive or non-routine procedures are performed.

The AI system is used solely for research purposes, including model development and evaluation. Outputs generated by the system are not returned to clinicians or patients and are not used to influence diagnosis, treatment, or clinical decision-making. All retinal imaging utilized in this study is obtained using FDA-cleared, commercially available devices as part of routine clinical care. No investigational hardware devices are used. Based on these factors, the study is considered IDE-exempt and does not require submission of an Investigational Device Exemption to the FDA.

16. Informed Consent Process

Written informed consent and HIPAA authorization will be obtained from all participants before inclusion in the study. Remote consent procedures may be used when appropriate. The study will enroll only adults with capacity to consent and will not enroll minors or adults unable to provide informed consent under this protocol. E-Consent may be used for this study.

17. Study Oversight and Data Monitoring

The study will be overseen by the Principal Investigator, who is responsible for ensuring compliance with the protocol, regulatory requirements, and data protection standards. Given the minimal risk nature of the study, a formal Data Safety Monitoring Board is not required. Data quality and integrity will be monitored by the study team through periodic review of data completeness, accuracy, and security. Any protocol deviations or adverse events will be documented and reported in accordance with institutional and IRB requirements.

18. References

1. Zekavat SM, Jorshery SD, Rauscher FG, Horn K, Sekimitsu S, Koyama S, Nguyen TT, Costanzo MC, Jang D, Burt NP, et al. Phenome- and genome-wide analyses of retinal optical coherence tomography images identify links between ocular and systemic health. *Sci Transl Med*. 2024 Jan 24;16(731):eadg4517.
2. Poplin R, Varadarajan AV, Blumer K, Liu Y, McConnell MV, Corrado GS, Peng L, Webster DR. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nat Biomed Eng*. 2018 Mar;2(3):158-164.
3. Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, Venugopalan S, Widner K, Madams T, Cuadros J, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA*. 2016 Dec 13;316(22):2402-2410.
4. Ting DSW, Peng L, Varadarajan AV, Keane PA, Burlina PM, Chiang MF, Schmetterer L, Pasquale LR, Bressler NM, Webster DR, et al. Deep learning in ophthalmology: The technical and clinical considerations. *Prog Retin Eye Res*. 2019 Sep;72:100759.

5. Cheung CYL, Ikram MK, Chen C, Wong TY. Imaging retina to study dementia and stroke. Prog Retin Eye Res. 2017 Mar;57:89-107.

17. Principal Investigator Signature

Principal Investigator Signature: _____

Date: _____