ACCESS: AI for pediatriC diabetiC Eye examS Study

NCT05131451

Date: 9/5/2023

FINAL PROTOCOL - TABLE OF CONTENTS

A Introduction

A1 Study Abstract and Background

Diabetic retinopathy (DR) is a complication of diabetes and a leading cause of blindness in adults as early as age 20. Youth with type 1 and type 2 diabetes are at risk for DR, yet only 35-72% of youth undergo recommended DR screening exams, with minority youth and children from lower socioeconomic backgrounds less likely to undergo screening as compared to their white counterparts.[1]

Early detection of diabetic retinopathy through screening prevents progression to vision loss. While DR screening is traditionally fulfilled by a referral to an eye care provider (ECP) for a dilated eye exam, use of nonmydriatic fundus cameras with new and innovative autonomous artificial intelligence (AI) systems have recently been developed for DR screening. Autonomous AI performed at the point-of-care (POC) provides an immediate result, and was FDA approved for use in adults in 2018.[2] Autonomous AI technology has been validated against patient outcome, demonstrating an 87% sensitivity and 90% specificity in detecting referable DR in adults,[2] compared to 30-40% sensitivity for clinical experts,[3] with equal safety and effectiveness for all races, ethnicities and ages, and higher diagnostic accuracy than clinical experts for detecting DR and DME. In a pilot prospective study at our pediatric diabetes center using AI technology for DR screening, we demonstrated 85.7% sensitivity and 79.3% specificity in detecting referable diabetic retinopathy, and an improved adherence to screening from 49% to 95%.[4]

We hypothesize that POC autonomous AI in the diabetes care setting will increase DR screening rates in youth with diabetes and mitigate disparities in access to screening. In this study, we will determine if point of care autonomous AI improves screening adherence compared to standard in person eye care professional exams in a randomized control trial.

A2 Primary Hypothesis

We hypothesize that POC Autonomous AI screening will increase DR screening rates in comparison to ECP (Aim 1a), and will improve follow-up with ECP in the case of abnormal findings (Aim 1b).

A3 Purpose of the Study Protocol

We will perform a randomized control trial to determine if autonomous AI increases DR screening rates in comparison to ECP. ECP-based dilated eye exams are the standard of care, and thus will serve as the control arm in this study. Autonomous AI is an acceptable comparator, because it has been validated against patient outcome in the adult diabetes population,[2,5] and data from a pilot study using autonomous AI off-label in pediatrics demonstrated diagnostic accuracy, and sufficient sensitivity and specificity for detection of DR in the pediatric population.[4] The alternative strategy that we considered was telemedicine or teleretinal networks, which have been used for more than 20 years, but these systems have not been validated against patient outcome (ETDRS). Further, while reading centers have demonstrated consistent fundus image interpretation, the real-world use of networks with various trained readers (optometrists, ophthalmologists

and retina specialists) can result in variable interpretation.[3] Thus we have chosen to compare autonomous AI to ECP.

B Study Objectives

B1 Primary Aim

To determine if point-of-care autonomous AI improves screening adherence compared to standard in-person eye care professional exams in a randomized control trial.

B2 Secondary Aim

To assess follow-up rates with ECP in the standard of care arm, compared to participants in the AI arm who screen positive and receive a referral to ECP for further evaluation.

C Study Design

C1 Overview of Study Design

This is a hypothesis-driven, pre-registered, prospective parallel, randomized control trial with a 1:1 allocation ratio where participants will be randomized to the standard of care or the autonomous AI arm.

The control arm is the standard of care referral to an eye care provider for a diabetic eye exam. In this study, to add *rigor, ethics* and maximum follow-up at ECP, participants in this arm will receive a scripted, brief educational intervention including the following 3 points: a) risks for complications of diabetes, b) what a DR screening exam entails and where it can be done, and c) reminder to have results faxed to their endocrine provider. We propose that this addresses the ethical concern of poor baseline completion of the diabetic eye exam amongst people with diabetes.

In the intervention arm, or autonomous AI arm, participants will undergo point of care diabetic eye exams using autonomous AI in the pediatric diabetes clinic, and will receive immediate results from autonomous AI. If the screen is normal, they have completed their screening. If the AI screen is abnormal, they will then be referred to ECP for further examination and will receive a scripted educational intervention. If the images are insufficient for interpretation, they will be referred to ECP for further examination and will receive a scripted educational intervention.

Followup: After randomization in the study, participants will have 6 months to complete the diabetic eye exam (in the control arm) or follow-up eye exam (in the intervention arm if AI abnormal). If the exam is not complete by 6 months, or the participant cannot be reached to determine completion of the exam, it will be considered not done.

C2 Subject Selection and Withdrawal

2.a Inclusion Criteria

- T1D: 11 years of age or older or in puberty, with diabetes for at least 3 years (ADA guidelines)[6]
- T2D: at diagnosis and thereafter (ADA guidelines)
- No known diabetic retinopathy
- No diabetic retinopathy exam within the last 6 months

2.a Exclusion Criteria

- Known diabetic eye disease

2.b Subject Recruitment Plans and Consent Process

Individual(s) responsible for approaching participant(s): Research coordinators

Where and when recruitment will take place:
Participants will be recruited, screened for eligibility, and consented in a private clinic/room to ensure privacy.

Consent process:
Participants will read through the consent form with the research coordinator, have time to review it and ask questions about the study and study procedures.

2.c Randomization Method and Blinding

To prevent selection bias and ensure sample size balance between the groups and sites, a stratified randomization (by site) scheme was developed with participants randomized in permutated block schedules of 4 and 6. Within each block, participants are randomized with a 1:1 allocation ratio to the control group and intervention group. This randomization sequence was created by a statistician unaffiliated with the study to ensure masking, and then another unaffiliated statistician entered the randomization scheme into REDCAP's randomization software.[7] After consent, the research coordinator will enter the participant location, and the randomization allocation is generated. All parties are masked to the allocation until the participant is randomized, and then all parties are unmasked.

2.d Risks and Benefits

This study involves no medical risks to the participants because of the non-invasive nature and lack of use of dilating eye drops for fundus photography. The only potential risk is related to privacy issues, should data with identifiers become non-secure.

Confidentiality: There is the risk that psychological, emotional, financial, social, and legal risks might result if confidentiality cannot be maintained in this study. All study team members are HIPPA trained and will take every step to respect participants' privacy and

protect their confidentiality throughout the study. We share the information gathered in the study only with the people who need to know this information. All information gathered during this study will be kept in a secure HIPAA compliant database, REDCap.

Benefit: Undergoing diabetic eye exam screening can lead to possible detection of diabetic retinopathy and allow for appropriate timely management.

2.e Early Withdrawal of Subjects

Participants may withdraw from the study at any time by notifying the study team.

2.f When and How to Withdraw Subjects

The participant may choose to withdraw from the study. The study visit is a one-time study visit, so once the participant is enrolled, if they choose to withdraw, it will not affect study procedures. It will also not impact the course of the participant's clinical care.

2.g Data Collection and Follow-up for Withdrawn Subjects

Data collected from subjects will remain in the dataset as this is an intent to treat analysis, but no follow-up will be conducted on withdrawn subjects.

D Study Procedures

D1 Screening for Eligibility

Patients being seen in the diabetes center will be pre-screened for eligibility by the research team based on the inclusion criteria. Eligibility will be confirmed with the patient's diabetes provider at the time of the clinic visit, and with the potential participant based on the inclusion criteria. The study coordinator will confirm that the participant has not had a diabetic eye exam within the prior 6 months.

D2 Schedule of Procedures

If the patient is eligible and interested in the study, the research coordinator will meet with the patient and caregiver in an exam room for privacy and confidentiality. The research coordinator will explain the study and study procedures, read the informed consent form with the participant and caregiver, and allow time for questions on the study and consent form.
If the participant is less than 18 years of age, the parent will sign the consent form and the participant will sign the assent. If the participant is 18 years of age or over, the participant can sign the consent.

After consent is signed, a new record is entered in REDCap and the participant assigned a study ID, then the site is entered and the randomization allocation generated. Until randomization is assigned, the study coordinator and participant are masked to the

allocation. At the time of consent, 3 phone numbers are collected from the participant for future follow-up.

Participants will be randomized to one of two interventions:

1) **ECP + Educational Intervention.** The control arm will receive the standard of care referral to ECP for DR screening. To add rigor, ethics and maximum follow-up at ECP, participants in this arm will receive a scripted, brief educational intervention including the following 3 points: a) risks for complications of diabetes, b) what a DR screening exam entails and where it can be done, and c) reminder to have results faxed to their endocrine provider.
    a. Participants in the control arm will complete a survey after the ECP eye exam is complete.

2) **Autonomous AI.** Participants in the intervention arm will undergo POC DR screening using autonomous AI in the pediatric diabetes clinic, and will receive immediate results from autonomous AI. If the screen is normal, they have completed their screening. If the AI screen is abnormal, they will then be referred to ECP for further examination and will receive a scripted educational intervention stating the importance of eye care follow-up and to have results faxed to their endocrine provider. If the images are insufficient after 3 attempts, then they will be referred for eye care follow-up.
    a. Participants in the AI arm will complete a survey after the AI eye exam is complete.

3) *Follow-up:* Participants will have up to 6 months to complete the ECP diabetic eye exam (control arm) or follow-through eye exam after an abnormal AI result in the intervention arm.

Children with diabetes care are typically seen by their diabetes provider every 3 months. As part of routine diabetes intake, patients are asked if they have had an eye exam since the last visit and the date is recorded by the nurse or diabetes provider.
If a participant returns for diabetes care to the clinic within the 6-month follow-up window, and an eye exam is reported, the research coordinator will meet with the participant to complete a follow-up acceptability survey (paper and pencil or on a tablet). If the eye exam results are not in the medical chart, the research coordinator will contact the eye doctor's office to have the results faxed to the provider office.

Once the participant reaches their 6-month follow-up window and there is no documentation of the eye exam in the medical record, the study coordinator will approach the participant in person at the next diabetes clinic visit to determine if they completed an ECP visit, or contact the family by EHR-based secure messaging, or calls / voicemails to all 3 phone numbers provided upon enrollment. The eye exam will be considered complete if documentation of the eye exam is in the medical record, or the participant/caregiver reports the diabetic eye exam completed.
If the exam has not been completed by 6 months or the participant cannot be reached, it will be considered not done/unscreened.

D3 Autonomous AI diabetic eye exam procedure

In prior studies with pediatric patients,[4] pharmacologic dilation was not required; therefore the participant's eyes will *not* be pharmacologically dilated in this study. The autonomous AI system guides the operator to acquire two color fundus images of each eye, determined to be of adequate quality using an image quality algorithm, one each centered on the fovea and the optic nerve, and guides the operator to retake any images of insufficient quality. This process requires approximately 10 minutes, after which the autonomous AI system reports one of the following results within 60 seconds: "DED present, refer to specialist", "DED not present, test again in 12 months", or "insufficient image quality". The latter response will occur if the operator is unable to obtain images of adequate quality after 3 attempts.

The IDx-DR autonomous AI system used in this study is not labeled for youth <22 years, thus all images will be overread in a deferred manner by a board certified retina specialist at the end of the study. Study procedures and follow-up are determined by the AI system results.

D4 Safety and Adverse Events

4.a Safety and Compliance Monitoring

Site investigators will monitor compliance with the protocol and good clinical practice (GCP) guidelines.

4.b Medical Monitoring for adverse events

Participants will be monitored for adverse events during the study visit and during the fundus photography.

4.c Definitions of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject.

4.d Classification of Events

- **Relationship**

Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

- **Severity**

The severity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate: Sufficient discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

4.e Data Collection Procedures for Adverse Events

All enrolled participants will be monitored for untoward incidents (e.g., “Adverse Events”) occurring during the study. The Principal Investigator (and other designated individuals, if necessary) will conduct regular monitoring for safety concerns and provide general oversight for human subject safety requirements during the study visit and fundus imaging. All adverse events that are anticipated or described in the informed consent form will be logged appropriately and reported to the IRB on at least an annual basis (e.g., at continuing review).

4.f Reporting Procedures

Any Unanticipated Problems or unexpected “Serious Adverse Events” related to the study intervention and/or test fundus imaging and affecting the risk/benefit profile of the study, will be reported to the IRB promptly, and, in all cases, within 10 business days of discovery. Unplanned and non-emergent deviations from the IRB approved protocol will be logged and reported to the IRB annually at continuing review; all planned deviations will be submitted as a Change in Research to the IRB for approval and prior to implementation. All other event reporting requirements will be followed and all necessary parties will be notified of events/problems encountered in the study and/or changes in research, in accordance with all applicable regulations and guidelines.

4.g Adverse Event Reporting Period

Any Unanticipated Problems or unexpected “Serious Adverse Events” related to the study intervention and/or test article and affecting the risk/benefit profile of the study, will be reported to the IRB promptly, and, in all cases, within 10 business days of discovery.

4.h Post-study Adverse Event

Not applicable

E. Statistical Plan

E1. Sample Size Determination and Power

The following power calculations assume 80% power and a 2-tailed type 1 error of 0.05. Data from the pilot study in pediatrics showed that of all children in the study, only 49% reported a prior diabetic eye exam, and this increased to 95% with the implementation of POC AI screening.[4] National data show that 42% of youth with T2D and 66% of youth with T1D had a diabetic eye exam by 6 years after initial diabetes diagnosis,[1] and our preliminary data showed that of youth who met ADA criteria for DR screening, 66% had a prior diabetic eye exam (46% non-white, 85% white youth). We assume that adding the educational intervention will raise the ECP rate to 60%. Randomization and study visit occur at the same time so there is little risk of attrition, and thus the study sample size will not be expanded to account for attrition. To show difference in proportion of who gets screened we assess a 20% difference to be clinically relevant between the two

strategies. Committing to demonstrating this difference results in a sample size of 164 (n=82 ECP, n=82 AI).

E2. Interim Monitoring and Early Stopping

One interim efficiency analysis for efficacy is planned. Using the alpha spending function with O'Brien and Fleming stopping rules, we will stop the trial if we show efficacy at the $p < 0.0054$ level. To adjust for the interim look, if the trial continues to the planned full sample size, the threshold for significance will be $p < 0.0492$.
Although consideration may be given to stop the study early because of an apparent beneficial treatment effect, early termination for efficacy will be considered with caution because of the degree of uncertainty with regard to the long-term benefit of treatment even if a short-term benefit seems apparent prior to the completion of the study. This will be determined by the independent DSMB committee.

E3. Analysis Plan

Primary outcome variable.
The primary outcome is the *proportion* of participants who get screened between AI and ECP. The comparison will be assessed using a Pearson's chi-square test (primary outcome) and logistic regression (adjusting for covariates).

Secondary outcome variables.
The secondary outcome is follow-up at ECP in each arm, comparing proportion of participants who arrive at ECP for DR screening in the control arm, to the proportion of participants in the AI arm who have an abnormal AI screening, are referred to ECP for follow-up, and arrive at ECP. This will be analyzed using a Pearson's chi-square test and logistic regression (adjusting for covariates).

E3. Statistical Methods
Statistical analyses will be performed using Stata 15.1 (Statacorp, College Station, TX). The primary and secondary outcomes will be further analyzed (in addition to above) using multivariate logistic regression analyses in order to examine the relationship between demographic characteristics and the outcomes. Additionally, multivariable logistic regression analyses will assess the odds of having a previous diabetic eye exam, adjusting for known covariates associated with diabetic eye disease. This will be an intent to treat analysis; all participants will be analyzed.

E4. Missing Outcome Data

Dataset will be assessed for missing-ness and noted in results.

E5. Unblinding Procedures

Not applicable

F. Data Handling and Record Keeping

F1. Confidentiality and Security

All data for this study will be recorded and stored in REDcap through Johns Hopkins Medicine.

F2. Records Retention

Informed consent documents will be securely stored in a locked file cabinet within a locked office. Informed consents will also be scanned into the participant's electronic medical record. Eye exam results from the AI camera will be uploaded into the Media section of the participant's electronic medical record in Epic.

G. Study Administration

G1. Organization and Participating Centers

Johns Hopkins Pediatric Diabetes Center
Mount Washington Pediatric Hospital Diabetes Center

G2. Funding Source

Funding for this study is provided by the National Eye Institute of the National Institutes of Health under Award Number R01EY033233 (PI: Wolf), and the Diabetes Research Connection (PI: Wolf).

G3. Subject Stipends or Payments

Participants received a $25.00 gift card, and a parking pass at the study visit.

E References

1. Wang SY, Andrews CA, Gardner TW, Wood M, Singer K, Stein JD. Ophthalmic Screening Patterns Among Youths With Diabetes Enrolled in a Large US Managed Care Network. JAMA Ophthalmol 2017;135:432-8.
2. Abramoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. NPJ Digit Med 2018;1:39.
3. Liu Y, Rajamanickam VP, Parikh RS, et al. Diabetic Retinopathy Assessment Variability Among Eye Care Providers in an Urban Teleophthalmology Program. Telemed J E Health 2019;25:301-8.
4. Wolf RM, Liu TYA, Thomas C, et al. The SEE Study: Safety, Efficacy, and Equity of Implementing Autonomous Artificial Intelligence for Diagnosing Diabetic Retinopathy in Youth. Diabetes Care 2021;44:781-7.

5. Verbraak FD, Abramoff MD, Bausch GCF, et al. Diagnostic Accuracy of a Device for the Automated Detection of Diabetic Retinopathy in a Primary Care Setting. Diabetes Care 2019;42:651-6.
6. 13. Children and Adolescents: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44:S180-s99.
7. REDCap.