# CLINICAL STUDY PROTOCOL

# Observational Study of Individual or Group Template

**Undiagnosed Diabetic Retinopathy: Using Participatory Science to Design an Intervention for Patients at High-Risk for Blindness**

**Protocol Number**

2000031731

NCT05188703

**Protocol Version**

03/25/2022

Version 3

**Confidentiality Statement:**

# Synopsis

Purpose

Evidence-based treatment for Diabetic retinopathy (DR) established 30 years ago decreases the likelihood of blindness by 50%.[4] Outcomes are even better now with emerging therapies and technology.[45] Diabetes remains the leading cause of new cases of legal blindness.[1,2] This study is *significant* because it investigates the gap between published guidelines and the population that continues to go blind despite well-established recommendations for screening. Our current model of screening for DR screens much of the population appropriately. There is an opportunity to improve DR screening by timely identification of persons at risk for preventable blindness. DR disproportionately impacts Non-Hispanic Blacks, Latinos, Native Americans, and lower socioeconomic communities.[14-16,46,47] Racial and ethnic minorities are less likely to be screened for DR,[9,10] have a higher prevalence of disease,[11-13] and more severe disease.[12-25] There is not a clear path toward decreasing these disparities beyond these data. This study addresses barriers to the implementation of evidenced-based treatment protocols by identifying modifiable patient and population-level challenges and building an intervention informed by community members and national data. It is a direct response to the "population health imperative" described by the National Academies of Science, Engineering, and Medicine.[48] Our study answers the National Eye Institute's Strategic Plan request to evaluate disparities by identifying barriers that prevent optimal treatment.[49] It is aligned with the NEI's mission to support research and training with respect to the preservation of sight. The National Institute on Minority Health and Health Disparities Research Framework provides the conceptual foundation for our work.[50] Our proposal identifies facets of the biologic, built, and sociocultural environments of the national population with undiagnosed DR. The national analysis informs a local individual-level intervention that addresses determinants associated with DR screening. The *scientific premise* of this study is the forty percent of persons with diabetes not screened despite established sight-saving treatment,[9] the known disparities in screening for DR,[9,10] and the increased prevalence of sight-threatening DR in Black, Latino, Native, and lower income Americans.[11]

**Primary Objective**

The primary objective of this study is to design and pilot a patient navigator program to increase screening for DR in a high-risk population.

**Secondary Objective**

To determine the feasibility and accessibility of a patient navigation program for persons at high-risk for DR.

**Study Design**

This is a pilot study of a patient navigator intervention for people living with diabetes and at high risk of diabetic blindness. We are assessing the feasibility and acceptability of the intervention in preparation for a clinical trial.

Components.

The SEEN Program will consist of three components: a clinical assessment, an educational experience, and patient navigator assessment and follow-up.

Clinical assessment. At the initial clinical visit, participants will be presented with the risks and benefits of the program and an informed consent will be obtained. Participants will undergo a complete dilated eye exam, fundus photography, and a point of care HbA1c

test. The eye examination will include visual acuity, intraocular pressure, slit lamp examination, and funduscopic examination. Fundus photography will be performed by a trained ophthalmic photographer on an Optos California widefield fundus camera. Funduscopic images will be read by a board-certified vitreoretinal surgeon. This is all considered standard of care for patients with diabetes. Classification of retinopathy will be determined by the international clinical diabetic retinopathy severity scale.[105]

Educational experience. Participants will be shown the educational audiovisual prototype. The content will provide education about DR and the importance of eye exams. The prototype will include text and audio. It will provide 10 minutes of content at a 5th grade level. A research assistant will be available to answer questions following the presentation. Questions beyond the knowledgebase of the research assistant will be directed to the principal investigator.

Patient navigator assessment and follow-up. A trained patient navigator from Project Access-New Haven, a local patient navigator organization, will conduct initial assessments and follow-up evaluations for participants. Initial visits will include an in-person assessment and the Rapid Estimate of Adult Literacy in Medicine-Short Form literacy evaluation[106]. Individual barriers to DR screening will be documented. Challenges will be addressed to the best of the navigator's abilities. For example, if the participant is experiencing transportation difficulties, the patient navigator team will offer public transportation options and transportation alternatives covered by the participant's insurance. The SEEN patient navigator will contact participants quarterly via telephone to evaluate ongoing challenges for the first year. After the first year, participants will be contacted semi-annually. Contact will be tracked using the Klara secure patient management system. After 2 years in the program, participants will be asked to complete an exit interview survey (Exit Interview Survey). During the interview, participants will be asked to give their thoughts on the structure of the program, the benefits of the program, and areas for improvement.

**Study Date Range and Duration**

The study will begin January 2022 and we anticipate recruitment will continue for 12 months. Participants enrolled in the study will be followed for 24 months post enrollment.

**Number of Study Sites**

Single site, Yale Eye Center

**Primary Outcome Variables**

The primary independent variable of interest will be eye care utilization at 18 months. Participants that have not returned for an eye examination by 18 months will be considered underutilizers. Those that have seen an eye care provider in the period after the initial assessment before 18 months will be considered normal utilizers. Sociodemographic covariates will include age, gender, education level, and health insurance status. Clinical covariates will include visual acuity, intraocular pressure, presence and stage of diabetic retinopathy, non-healing foot ulcers, kidney failure, dialysis, and laboratory values: HbA1c, systolic and diastolic blood pressure. Covariates not included in clinical assessment will be abstracted by EMR chart review. Neighborhood level variables will be obtained from available census data based on participant address. Patient navigation variables include time spent navigating individual participants, number of touches (phone calls, meetings, etc.) required to address needs, and outstanding barriers not addressed by patient navigators.

**Secondary and Exploratory Outcome Variables (if applicable)**

*Feasibility.* Feasibility will be determined by the ease of enrollment and recruitment, the time required for patient navigators to appropriately address participant needs, and the ability to meet the needs of the participants. The ease of recruitment will be determined by the number available potential participants identified in the EMR, the ease of eligible participant identification, and the amount of time required to recruit participants. The first ten participants recruited will provide initial data on participant needs. The time required by patient navigators to navigate each participant, the number of touches required to address participant needs, and the outstanding barriers left unaddressed by patient navigators will be identified using the Klara patient management system. At the end of the program, we will calculate the percentage of the participants remaining in the program and attempt to identify the reasons we were unable to maintain their enrollment.

*Acceptability.* The first ten participants will be administered a semi-structured interview to assess acceptability at the second quarterly patient navigator follow-up. The interview guide (Participant Acceptability Interview Guide) will address barriers to and facilitators of participation in the program and opportunities for improvement. Interviews will be recorded, transcribed, and organized into themes for evaluation by the research team. The patient navigators will be asked to evaluate the program in a semi-structured format after 6 months (Patient Navigator Interview Guide). These data will be shared in aggregate with the stakeholder design team and the Center for Research and Engagement Steering Committee. The Program will be optimized based on findings and the committee assessments.

**Study Population**

Patients ages greater than or equal to 18 years with diabetes in the Yale-New Haven Health system are eligible. Patients who have not seen an eye care provider within the last year, but have seen other providers, will be designated as under-utilizers of eye care. Those that have seen an eye care provider within the last year will be designated as normal utilizers.

New Haven is most demographically similar to the United States based on age, educational attainment, and race and ethnicity.[107] New Haven is 33% Black, 27% Hispanic, and 32% White according to the 2016 Greater New Haven Community Index.[108] These demographics support the generalizability of our results and the probability that we will recruit a diverse sample of participants.

**Number of Participants**

Sixty participants will be recruited. This is a pilot program to evaluate feasibility and accessibility. Power calculation will be reserved for randomized controlled clinical trial preparation in the future. We used a confidence interval approach109 to determine our pilot sample size based on an $\alpha=0.05$, upper one-sided 80% confidence-limit, 15% estimated difference detected, and a final control group participation of 50%. The pilot sample size at an 80% confidence interval is 32 participants. Sample size for a future main trial is 338 participants. We will recruit sixty participants to allow for drop-out and loss to follow-up in a population with a history of underutilization.

**Study Schedule**

Baseline assessment

Follow-up 3, 6, 9, 12, 18 months post enrollment

Exit interview from the program 24 months post enrollment

# Protocol Revision History

| Version Date | Summary of Substantial Changes |
|---|---|
| 11/17/2021 | Initial application |
| | |
| | |

# Statement of Compliance

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to the Common Rule at 45CFR46 (human subjects) and other applicable government regulations and Institutional research policies and procedures.

# Abbreviations

| Abbreviation | Explanation |
|---|---|
| **DR** | **Diabetic retinopathy** |

# Glossary of Terms

| Glossary | Explanation |
| --- | --- |

# Table of Contents

# 1 Background/Literature Review

## 1.1 Background

### RESEARCH STRATEGY

### SIGNIFICANCE

Evidence-based treatment for DR established 30 years ago decreases the likelihood of blindness by 50%.[4] Outcomes are even better now with emerging therapies and technology.[45] Diabetes remains the leading cause of new cases of legal blindness.[1,2] This study is *significant* because it investigates the gap between published guidelines and the population that continues to go blind despite well-established recommendations for screening. Our current model of screening for DR screens much of the population appropriately. There is an opportunity to improve DR screening by timely identification of persons at risk for preventable blindness. DR disproportionately impacts Non-Hispanic Blacks, Latinos, Native Americans, and lower socioeconomic communities.[14-16,46,47] Racial and ethnic minorities are less likely to be screened for DR,[9,10] have a higher prevalence of disease,[11-13] and more severe disease.[12-25] There is not a clear path toward decreasing these disparities beyond these data. This study addresses barriers to the implementation of evidenced-based treatment protocols by identifying modifiable patient and population-level challenges and building an intervention informed by community members and national data. It is a direct response to the “population health imperative” described by the National Academies of Science, Engineering, and Medicine.[48] Our study answers the National Eye Institute’s Strategic Plan request to evaluate disparities by identifying barriers that prevent optimal treatment.[49] It is aligned with the NEI’s mission to support research and training with respect to the preservation of sight. The National Institute on Minority Health and Health Disparities Research Framework provides the conceptual foundation for our work.[50] Our proposal identifies facets of the biologic, built, and sociocultural environments of the national population with undiagnosed DR. The national analysis informs a local individual-level intervention that addresses determinants associated with DR screening. The *scientific premise* of this study is the forty percent of persons with diabetes not screened despite established sight-saving treatment,[9] the known disparities in screening for DR,[9,10] and the increased prevalence of sight-threatening DR in Black, Latino, Native, and lower income Americans.[11]

1. Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2005.

2. Fong DS, Aiello L, Gardner TW, et al. Diabetic retinopathy. Diabetes Care. 2003;26(1):226-229.

3. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103(12):1796-1806.

4. Techniques for scatter and local photocoagulation treatment of diabetic retinopathy: Early Treatment Diabetic Retinopathy Study Report no. 3. The Early Treatment Diabetic Retinopathy Study Research Group. Int Ophthalmol Clin. 1987;27(4):254-264.

5. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study Report no. 4. The Early Treatment Diabetic Retinopathy Study Research Group. Int Ophthalmol Clin. 1987;27(4):265-272.

6. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1987;94(7):761-774.

7. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2010;117(6):1064-1077 e1035.

8. Diabetic Retinopathy Study Research Group. Report Number 6. Design, methods, and baseline results. Invest Ophthalmol Vis Sci. 1981; 21:147-226.

9. Shi Q, Zhao Y, Fonseca V, Krousel-Wood M, Shi L. Racial disparity of eye examinations among the U.S. working-age population with diabetes: 2002-2009. Diabetes Care. 2014;37(5):1321-1328.

10. Elam AR, Lee PP. High-Risk Populations for Vision Loss and Eye Care Underutilization: A Review of the Literature and Ideas on Moving Forward. Survey of Ophthalmology. 2013;58(4):348-358.

11. Zhang X, Saaddine JB, Chou CF, et al. Prevalence of diabetic retinopathy in the United States, 2005- 2008. Jama. 2010;304(6):649-656.

* The full reference list as included at the end of this application.

### 1.2 Prior Experience (if applicable)

The PI, Dr. Nwanyanwu is a board-certified, subspecialty-trained vitreoretinal surgeon. Her past research in diabetic retinopathy [28,39,43] and her review articles on contextual factors [40] and community engagement [44] have prepared her to carry out this pilot for her K23 career development award.

Specific Aim 1 (completed) and Specific Aim 2 (IRB Protocol# 2000029860) were the foundation for this pilot study.

Publication on Aim 1: Nwanyanwu KMJH, Nunez-Smith M, Gardner TW, Desai MM. Awareness of Diabetic Retinopathy: Insight From the National Health and Nutrition Examination Survey. Am J Prev Med. 2021 Dec;61(6):900-909. doi: 10.1016/j.amepre.2021.05.018. Epub 2021 Aug 21. PMID: 34426057; PMCID: PMC8608699.

**Specific Aim 1: Determine national prevalence of undiagnosed DR with a focus on racial and ethnic disparities and geospatial variation.**

*Scientific premise for Specific Aim 1.* The population with undiagnosed DR is the population that is not being screened appropriately. Undiagnosed DR is present in persons with diabetes who have not had an eye exam within one year, who have DR on examination, and who do not know that they have DR. Our hypothesis is that based on the natural history of DR[51] this population is more vulnerable to advanced disease and blindness. These patients have not been diagnosed with DR. They are less likely to undergo appropriately timed treatment and are at increased risk for blindness. The disparities in screening[9] and in the prevalence of DR[11] underlie our hypothesis that there will be a disproportionate number of racial and ethnic minorities in the undiagnosed DR population.

Undiagnosed DR has not been examined on a national level. In a population-based, NEI-funded, cross-sectional study, the Los Angeles Latino Eye Study (LALES) evaluated a largely Mexican-American population in six Los Angeles census tracts for undetected eye

disease.[26] The study diagnosed undetected eye disease in participants who had diabetic retinopathy, age-related macular degeneration, glaucoma, cataracts, or refractive error on examination and did not report that history during the interview. Nearly 63% had undetected eye disease. This was a large, well-designed study that demonstrated the magnitude of undiagnosed aggregated eye disease in a minority population. We leverage this opportunity to disaggregate these diseases and focus on undiagnosed DR on a national level. Several large epidemiologic studies in ophthalmology have addressed the prevalence of DR[52-57] and disparities in eye disease.[56,58] A PubMed literature search did not reveal any others that evaluated undiagnosed DR.

**Specific Aim 2: Design and pilot a patient navigator program for those at high-risk for DR.**

*Scientific premise of Specific Aim 2.* Risk stratification facilitates screening in patients at the highest risk for disease. The Diabetes Control and Complications Trial demonstrated the benefit of intensive glycemic control in decreasing the likelihood of DR.[59] Participants with the least glycemic control were at the highest risk for DR. Our group sought to determine which factors were associated with the most sight-threatening form of DR. We identified the factors associated with progression to the most sight-threatening form of DR using a large managed care database.[28] We built and internally validated a risk calculator based on our findings and known risk factors from large epidemiologic studies. The risk calculator accurately predicted progression. There is a gap in the literature as to how risk stratification can benefit population-level DR screening in those at high-risk. Our proposal leverages the opportunity to use the risk calculator as a risk stratification tool.

The use of patient navigators has potential to increase DR screening and decrease disparities. Patient navigators facilitated cancer screen in low income communities[60-70], racial and ethnic minority populations[71-79], and other high-risk populations.[80]

# 2 Rationale/Significance

## 2.1 Rationale and Study Significance

Evidence-based treatment for DR established 30 years ago decreases the likelihood of blindness by 50%. [4] Outcomes are even better now with emerging therapies and technology. [45] Diabetes remains the leading cause of new cases of legal blindness.[1,2] This study is significant because it investigates the gap between published guidelines and the population that continues to go blind despite well-established recommendations for screening. Our current model of screening for DR screens much of the population appropriately. There is an opportunity to improve DR screening by timely identification of persons at risk for preventable blindness. DR disproportionately impacts Non-Hispanic Blacks, Latinos, Native Americans, and lower socioeconomic communities. [14-16,46,47] Racial and ethnic minorities are less likely to be screened for DR,[9,10] have a higher prevalence of disease,[11-13] and more severe disease.[12-25] There is not a clear path toward decreasing these disparities beyond these data. This study addresses barriers to the implementation of evidenced-based treatment protocols by identifying modifiable patient and population-level challenges and building an intervention informed by community members and national data. It is a direct response to the “population health imperative” described by the National Academies of Science, Engineering, and Medicine. [48] Our study answers the National Eye Institute’s Strategic Plan request to evaluate disparities by identifying barriers that prevent optimal treatment.[49] It is aligned with the NEI’s mission to support research and training with respect to the preservation of sight. The National Institute on Minority Health and Health Disparities Research Framework provides the conceptual foundation for our work.[50] Our proposal identifies facets of the biologic, built, and sociocultural environments of the national population with undiagnosed DR. The national analysis informs a local individual-level intervention that addresses determinants associated with DR screening. The scientific premise of this study is the forty percent of persons with diabetes not screened despite established sight-saving treatment,[9] the known disparities in screening for DR,[9,10] and the increased prevalence of sight-threatening DR in Black, Latino, Native, and lower income Americans.[11]

## 2.2 Purpose of Study/Potential Impact

The use of patient navigators has potential to increase DR screening and decrease disparities. Patient navigators facilitated cancer screening in low income communities [60-70], racial and ethnic minority populations [71-79], and other high-risk populations.[80] Patient navigators for diabetic populations helped patients navigate the health care system [81-86], connected patients to community resources, [87] and improved glycemic control.[82,88] Unpublished institutional KL-2-funded research identified individual, institutional, and structural determinants of DR screening in a predominantly racial and ethnic minority patient population evaluated in local federally qualified health centers (See preliminary studies).[31] Barriers to care exist in patients at high-risk for DR. Patient navigators have been used in similar populations to address similar barriers. Our review of the literature did not reveal any studies of patient navigators in DR screening. Our pilot study examines the feasibility and accessibility of patient navigation program for persons at high-risk for DR.

## 2.3 Potential Risks and Benefits

### 2.3.1 Potential Risks

The expected risks for each of these studies are minimal. The potential risks are loss of confidentiality and stress and anxiety related to interviews and survey evaluation. All audio

and survey information will be kept on password-protected, encrypted, University computers to decrease the likelihood of breach of confidentiality.

Any violation will be immediately reported to the Yale University Institutional Review Board. Participants will be informed that if they wish to stop the interview or survey at any time, they may without consequence.

### 2.3.2 Potential Benefits

Individual participants may benefit from engagement in eye care and screening for diabetic retinopathy. The development of an engagement strategy for those at high-risk for diabetic retinopathy has the potential to decrease blindness from diabetic eye disease.

# 3 Study Purpose and Objectives

## 3.1 Hypothesis

Our central hypothesis is that we can create a feasible and acceptable program to increase Diabetic Retinopathy screening in those at high-risk for DR.

## 3.2 Primary Objective

The primary objective of this study is to design a patient navigator intervention for those at high risk for Diabetic Retinopathy, informed by a national analysis of undiagnosed DR and lock a community stakeholders.

## 3.3 Secondary Objective

Feasibility. Feasibility will be determined by the ease of enrollment and recruitment, the time required for patient navigators to appropriately address participant needs, and the ability to meet the needs of the participants. The ease of recruitment will be determined by the number available potential participants identified in the EMR, the ease of eligible participant identification, and the amount of time required to recruit participants. The first ten participants recruited will provide initial data on participant needs. The time required by patient navigators to navigate each participant, the number of touches required to address participant needs, and the outstanding barriers left unaddressed by patient navigators will be identified using the Klara patient management system. At the end of the program, we will calculate the percentage of the participants remaining in the program and attempt to identify the reasons we were unable to maintain their enrollment.

Acceptability. The first ten participants will be administered a semi-structured interview to assess acceptability at the second quarterly patient navigator follow-up. The interview guide (Appendix D, Participant Acceptability Interview Guide) will address barriers to and facilitators of participation in the program and opportunities for improvement. Interviews will be recorded, transcribed, and organized into themes for evaluation by the research team. The patient navigators will be asked to evaluate the program in a semi-structured format after 6 months (Appendix E, Patient Navigator Interview Guide). These data will be shared in aggregate with the stakeholder design team and the Center for Research and Engagement Steering Committee. The Program will be optimized based on findings and the committee assessments.

# 4 Study Design

### 4.1.1 General Design Description

Components. The SEEN Program will consist of three components: a clinical assessment, an educational experience, and patient navigator assessment and follow-up.

Clinical assessment. At the initial clinical visit, participants will be presented with the risks and benefits of the program and an informed consent will be obtained. Participants will undergo a complete dilated eye exam, fundus photography, and a point of care HbA1c test. The eye examination will include visual acuity, intraocular pressure, slit lamp examination, and funduscopic examination. Fundus photography will be performed by a trained ophthalmic photographer on an Optos California widefield fundus camera. Funduscopic images will be read by a board-certified vitreoretinal surgeon. This is all standard of care for people with diabetes. Classification of retinopathy will be determined by the international clinical diabetic retinopathy severity scale.[105] Educational experience. Participants will be shown an educational audiovisual prototype. The content will provide education about DR and the importance of eye exams. The prototype will include text and audio. It will provide 10 minutes of content at a 5th grade level. A research assistant will be available to answer questions following the presentation. Questions beyond the knowledgebase of the research assistant will be directed to the principal investigator.

Patient navigator assessment and follow-up. A trained patient navigator from Project Access of New Haven, Inc., a local patient navigator organization, will conduct initial assessments and follow-up evaluations for participants. Initial visits will include an in-person assessment (Project Navigator In-Person Assessment) and the Rapid Estimate of Adult Literacy in Medicine-Short Form literacy evaluation [106]. Individual barriers to DR screening will be documented. Challenges will be addressed to the best of the navigator's abilities. For example, if the participant is experiencing transportation difficulties, the patient navigator team will offer public transportation options and transportation alternatives covered by the participant's insurance. The SEEN patient navigator will contact participants quarterly via telephone to evaluate ongoing challenges for the first year. After the first year, participants will be contacted semi-annually. Contact will be tracked using the Klara secure patient management system. After 2 years in the program, participants will be asked to complete an exit interview survey (Exit Interview Survey). During the interview, participants will be asked to give their thoughts on the structure of the program, the benefits of the program, and areas for improvement.

### 4.1.2 Study Date Range and Duration

Recruitment will begin in January 2022. We anticipate recruitment will end 12 months after enrollment begins. Follow-up will continue until December 2024.

### 4.1.3 Number of Study Sites

**T**his is a single site study conducted at the Yale Eye Center.

## 4.2 Outcome Variables

### 4.2.1 Primary Outcome Variables

The primary independent variable of interest will be eye care utilization at 18 months. Participants that have not returned for an eye examination by 18 months will be considered underutilizers. Those that have seen an eye care provider in the period after the initial assessment before 18 months will be considered normal utilizers. Sociodemographic covariates will include age, gender, education level, and health insurance status. Clinical

covariates will include visual acuity, intraocular pressure, presence and stage of diabetic retinopathy, non-healing foot ulcers, kidney failure, dialysis, and laboratory values: HbA1c, systolic and diastolic blood pressure. Covariates not included in clinical assessment will be abstracted by EMR chart review. Neighborhood level variables will be obtained from available census data based on participant address. Patient navigation variables include time spent navigating individual participants, number of touches (phone calls, meetings, etc.) required to address needs, and outstanding barriers not addressed by patient navigators.

### 4.2.2 Secondary and Exploratory Outcome Variables

Feasibility. Feasibility will be determined by the ease of enrollment and recruitment, the time required for patient navigators to appropriately address participant needs, and the ability to meet the needs of the participants. The ease of recruitment will be determined by the number available potential participants identified in the EMR, the ease of eligible participant identification, and the amount of time required to recruit participants. The first ten participants recruited will provide initial data on participant needs. The time required by patient navigators to navigate each participant, the number of touches required to address participant needs, and the outstanding barriers left unaddressed by patient navigators will be identified using the Klara patient management system. At the end of the program, we will calculate the percentage of the participants remaining in the program and attempt to identify the reasons we were unable to maintain their enrollment.

Acceptability. The first ten participants will be administered a semi-structured interview to assess acceptability at the second quarterly patient navigator follow-up. The interview guide (Appendix D, Participant Acceptability Interview Guide) will address barriers to and facilitators of participation in the program and opportunities for improvement. Interviews will be recorded, transcribed, and organized into themes for evaluation by the research team. The patient navigators will be asked to evaluate the program in a semi-structured format after 6 months (Appendix E, Patient Navigator Interview Guide). These data will be shared in aggregate with the stakeholder design team and the Center for Research and Engagement Steering Committee. The Program will be optimized based on findings and the committee assessments.

## 4.3 Study Population

The study population are adults at high risk for diabetic retinopathy. This requires a diagnosis of diabetes and no eye exam in the past year. Adults with diabetes who do not have routine eye exams with dilation are at increased risk of preventable blindness.

### 4.3.1 Number of Participants

N = 60

We do not know how many participants we will need to screen to enroll 60 participants but anticipate enrolling 1 out of every 4 participants screened.

### 4.3.2 Eligibility Criteria/Vulnerable Populations

The RA will be trained to determine eligibility. They will contact the research manager or PI if unsure if participant is eligible or not.

To be eligible for inclusion in the study, an individual must meet all the following criteria:

- Adults aged 18 and over

- Diagnosis of diabetes and record of diagnosis in YNHHS Epic
- English-speaking
- No documented eye examination within 1 year of study enrollment
- High risk for diabetic retinopathy based on risk calculator evaluation

# 5 Study Methods/Procedures

## 5.1 Study Procedures

Participants will be recruited a variety of ways since we are targeting individuals who are not currently receiving eye care. We will advertise the study via flyers posted in clinics, internet/web postings on our lab's website, departmental newsletters, YCCI Recruitment Database, and social media. We will provide a Qualtrics survey link so a potential participant may "opt in" if they are interested in the study. An RA will then reach out via phone to screen for eligibility. Additionally, the Project Navigators employed by Project Access – New Haven will also refer potentially eligible patients who express interest in the study. Finally, we will request JDAT pull a list of all patients in EPIC who meet eligibility criteria. These are people in the health system diagnosed with diabetes who have not received eye exams in the past 12 months. They may or may not be former patients of the Yale Eye Center and/or the PI. Via MyChart, a message will be sent to potentially eligible participants. Participants will be able to opt in if they wish to be contacted about the study. YCCI will also send a recruitment letter to all potential participants with a phone number for the YCCI research recruitment team if they are interested in the study. YCCI will then pass interested participants to the study team. Participants will meet with an RA at the Yale Eye Center. First, the RA will explain the study, give the participant a chance to ask questions and sign consent. The RA will then complete a brief face sheet and baseline data collection with the participant. This visit with the RA should take about 20 minutes.

The RA will check the participant in for the A1c, eye exam, dilation, and fundus photography, as part of the standard of care for eye exams for people with diabetes. This part of the visit follows the operating procedures of the Yale Eye Center. Visits typically take 2-3 hours.

Before the participant leaves the Eye Center, the RA will give the participant the date and time of the appointment with the patient navigator at Project Access, register the participant in OnCore for study payment and answer any additional questions. This should only take about 5 minutes.

The participant will meet with a patient navigator and complete intake forms for Project Access. This visit will take about an hour.

At 3, 6, 9, 12, and 18 months after the enrollment visit, the participant will have an in-person or telephone visit with the patient navigator. These visits should take about 30 minutes each. After the completion of each of these visits, the visit will be recorded in OnCore and payment will be added to the participant's reloadable Bank of America debit card.

### 5.1.1 Data Collection

Contact information and participant payments will be entered into and processed through OnCore. Data will be recorded on paper forms and entered into Qualtrics. Participants will be assigned an identifier code to be used on all paper forms and in Qualtrics. Only the PI, research manager and research team will have access to the data and the linking identifier code for participants. Paper forms will be stored in a locked cabinet in the PI's locked office at 40 Temple Street.

### 5.1.2 Adverse Events Definition and Reporting

We do not anticipate any adverse events because of this research. The Yale University Institutional Review Board must approve the study before recruitment begins. Participants will be engaged in interviews and surveys and a routine eye exam. Medical information will be extracted from the electronic medical record. There are no medical or surgical interventions in our research program. Nonetheless, if an adverse event occurs, the contact information of the principal investigator and the research manager will be present on all informed consent documentation so that participants may easily contact the team.

## 5.2 Study Schedule

Intake/enrollment visit (120-180 minutes)

Patient navigator intake (30-60 minutes)

Patient navigation check ins at 3-, 6-, 9-, 12-, and 18-months post enrollment (15-30 minutes)

## 5.3 Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- Compound Authorization
-

### 5.3.1 Screening (if applicable)

Potential participants will be screened by the study RA. The RA will speak to the individual to confirm diabetes diagnosis, date of diagnosis, date of last eye exam.

### 5.3.2 Recruitment, Enrollment and Retention

Participants will be recruited a variety of ways since we are targeting individuals who are not currently receiving eye care. We will advertise the study via flyers posted in clinics, internet/web postings on our lab's website, departmental newsletters, YCCI Recruitment Database, and social media. We will provide a Qualtrics survey link so a potential participant may "opt in" if they are interested in the study. An RA will then reach out via phone to screen for eligibility. Additionally, the Project Navigators employed by Project Access – New Haven will also refer potentially eligible patients who express interest in the study. Finally, we will request JDAT pull a list of all patients in EPIC who meet eligibility criteria. These are people in the health system diagnosed with diabetes who have not received eye exams in the past 12 months. They may or may not be former patients of the Yale Eye Center and/or the PI. Via MyChart, a message will be sent to potentially eligible participants. Participants will be able to opt in if they wish to be contacted about the study. YCCI will also send a recruitment letter to all potential participants with a phone number for the YCCI research recruitment team if they are interested in the study. YCCI will then pass interested participants to the study team.

Participants will meet with an RA at the Yale Eye Center. First, the RA will explain the study, give the participant a chance to ask questions and sign consent. The RA will then complete a brief face sheet and baseline data collection with the participant. This visit with the RA should take about 20 minutes.

The RA will check the participant in for the eye exam, dilation, and fundus photography, as part of the standard of care for eye exams for people with diabetes. This part of the visit follows the operating procedures of the Yale Eye Center. Visits typically take 2-3 hours.

Before the participant leaves the Eye Center, the RA will give the participant the date and time of the appointment with the patient navigator at Project Access, give them the gift card for completing the intake assessment and answer any additional questions. This should only take about 5 minutes.

The participant will meet with a patient navigator and complete intake forms for Project Access. This visit will take about an hour.

At 3, 6, 9, 12, and 18 months after the enrollment visit, the participant will have an in-person or telephone visit with the patient navigator. These visits should take about 30 minutes each. After the completion of each of these visits, a gift card will be mailed to the participant.

### 5.3.3 Study Visits (if applicable)

**Intake/enrollment visit (120 – 180 minutes)**

- consent reviewed and signed
- contact information and baseline data collected
- point of care finger stick to test HbA1c
- eye exam with dilation and fundus photography

**Patient navigator intake (30-60 minutes)**

- complete patient navigation intake for Project Access

**Patient navigation check ins at 3-, 6-, 9-, 12-, and 18-months post enrollment (15-30 minutes)**

- These appointments will take place either over the phone or in person with a patient navigator from Project Access

## 5.4 Statistical Method

### 5.4.1 Statistical Design

Analysis.
Qualitative analysis. Semi-structured interviews will be recorded, transcribed, and organized using NVivo software. [110,111] Our research team will code the interviews and comments will be categorized into themes.[110-114] Themes will be presented to the stakeholder committee to guide the iterative development of the program. Community members will contribute their experiences and community members on the stakeholder committee will participate in the design of the intervention. The expected outcome of this analysis are themes associated with utilization of DR screening to inform the design of the program.
SEEN Program Analysis. The percentage of underutilization will be calculated in the cohort at 18 months. The presenting and incident DR diagnoses and stages will be compared between the underutilizer and normal utilizer groups. The mean and standard deviation will be calculated for continuous variables and numbers and percentages will be calculated for categorical variables. The Pearson's chi-squared test will be used to compare the underutilizers to the now normal utilizers. Multivariable logistic regression analyses will determine factors associated with underutilization. Models will be adjusted for age, race and ethnicity, gender, and health insurance status. All analyses will be performed using SAS

version 9.4 (SAS Institute Inc, Cary, NC). GIS will be used to analyze contextual factors associated with underutilization. Patient addresses will be geocoded, quantified, and categorized, which will allow for overlay of data onto existing locations. US Census data will be used to provide neighborhood level data including a calculated Neighborhood deprivation index[101]. ArcGIS software will be used to map the databases. Multivariate statistical analysis will be applied to the observation of each unit. The data will be examined using additive models and analysis of variance. The expected outcomes of these analyses are the identification of factors associated with underutilization, a comparison of the population of underutilizers and of normal utilizers, and a map of underutilization and normal utilization in our pilot population at a neighborhood level.

Underutilization cohort analysis. Participants identified retrospectively as underutilizers in the EMR will be compared to normal utilizers. The Pearson's chi-squared test will be used to compare the unadjusted rate of underutilization and normal utilizers. Multivariable logistic regression analyses will be performed to determine factors associated with underutilization. Models will be adjusted for age, race and ethnicity, gender, health insurance status. All analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). The expected outcome of this analysis will be identification of factors associated with utilization of DR screening and a comparison of utilization in a cohort of participants in the EMR.

Risk calculator external validation. A cohort of participants with DM will be identified at the beginning of the current EMR (2012). Those participants with normal utilization of eye care that do not have a diagnosis of DR will be followed through the EMR until the baseline assessment of the SEEN Program. Diagnosis of DR will be determined by ICD-9 and ICD-10 codes. The outcome will be development of DR by the end of the study period. We will apply the risk calculator to the cohort and compare the outcomes predicted by the risk calculator to the observed outcomes determined by chart review. A statistical comparison of observed and predicted risk in this population will determine the $R_2$ and the scaled Brier score, a measure of predictive accuracy, the concordance statistic, and discrimination slope.[115] All analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). The expected outcome of this analysis is the external validation of this risk calculator in a cohort without a baseline diagnosis of DR.

The expected outcomes of the approach to Specific Aim #2 are a piloted patient navigator program for those at high-risk for DR, a comparison of the factors associated with normal utilization and underutilization of DR screening in a retrospective cohort and a high-risk prospective cohort, and an external validation of our risk calculator.

### 5.4.2 Sample Size Considerations

SEEN Program sample size justification. Sixty participants will be recruited. This is a pilot program to evaluate feasibility and accessibility. Power calculation will be reserved for randomized controlled clinical trial preparation in the future. We used a confidence interval approach[109] to determine our pilot sample size based on an $\alpha=0.05$, upper one-sided 80% confidence-limit, 15% estimated difference detected, and a final control group participation of 50%. The pilot sample size at an 80% confidence interval is 32 participants. Sample size for a future main trial is 338 participants. We will recruit sixty participants to allow for drop-out and loss to follow-up in a population with a history of underutilization.

### 5.4.3 Planned Analyses

See section 5.4.1 above

### 5.4.4 Analysis of Subject Characteristics (if applicable)

See section 5.4.1 above

### 5.4.5 Interim Analysis (if applicable)

N/A

### 5.4.6 Handling of Missing Data

Every effort will be made to minimize missing data. For analysis, we will impute participants are underutilizers if outcomes are missing.

# 6 Trial Administration

## 6.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Consent forms will be Institutional Review Board (IRB)-approved and the participant/legally authorized representative (LAR) will be asked to read and review the document. The Research Associate will explain the research study to the participant and answer any questions that may arise. This conversation will take place in a private room.

Participants/LAR will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants/LAR should have the opportunity to discuss the study with their family or surrogates, or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants/LAR must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants/LAR for their records.
Assent will not be conducted.

## 6.2 Institutional Review Board (IRB) Review

This is a prospective research pilot with some retrospective data collection using surveys already in use by an established program at Yale New Haven Hospital, a standard of care eye exam for people with diabetes, and a point of care finger stick for HbA1c. The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.

A study closure report will be submitted to the IRB after all research activities have been completed.

## 6.3 Subject Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the

investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or, if applicable, sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Yale Secure Box. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Yale Secure Box.

### 6.4 Deviations/Unanticipated Problems

We do not anticipate any adverse events because of this research.

A protocol deviation is any noncompliance with the study protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the investigator to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the study sponsor, and the reviewing Institutional Review Board (IRB) per their policies.

Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and study sponsor, if applicable within 5 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and study sponsor within 5 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 5 business days of the IRB's receipt of the report of the problem from the investigator.

### 6.5 Data Quality Assurance

Data will be collected on paper forms and entered into Qualtrics. All research staff will be trained by the research manager on data collection and data entry. The research manager will perform quality audits on the data collected and entered regularly and provide feedback and retraining, if necessary.

### 6.6 Study Records

- JDAT data pulls from EPIC
- EPIC data extraction by research staff
- Compound Authorization
- Interview recordings
- SEEN face sheet
- Seen intake assessment
- Project Access intake assessment
- Results from the HbA1c
- Results from the eye exam, dilation, and fundus photography

### 6.7 Access to Source

Source data will be maintained per Medical Records policy in a password protected, secure, Health Insurance Portability and Accountability Act (HIPAA) compliant, web-based electronic database with a built-in audit trail.
Only Institutional Review Board (IRB) approved research team members who have current HIPAA and Collaborative Institutional Training Initiative (CITI) Good Clinical Practice (GCP) and human subjects protection training will be authorized to access records.

### 6.8 Data or Specimen Storage/Security

Contact information will be entered into OnCore. Data will be collected on paper forms and entered into Qualtrics managed by Yale. Paper forms will be stored in a locked cabinet in the PI's locked office. Electronic records will be stored in Yale managed OnCore, Qualtrics and Secure Box.

### 6.9 Retention of Records

Research records will be deidentified after data analysis is completed. The linking key will be destroyed after main publications are submitted and accepted in case we need to make corrections to manuscripts at the requests of reviewers.

### 6.10 Study Monitoring

The PI and research manager will monitor the study for accuracy and data completeness. They will take responsibility for correcting errors in data collection and data entry and ongoing training and auditing of research study staff.

### 6.11 Study Modification

All study modifications will be submitted to IRB and approved by the IRB prior to implementing the change.

### 6.12 Study Completion

Primary data completion should be completed in December 2024. The study should end in December 2025. The IRB will be notified when the study 1. Has completed recruitment, 2. Is in data analysis only and 3. Is completed.

### 6.13 Funding Source – Funded by National Eye Institute (NIH); 5K23EY030530

### 6.14 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by Yale's COI Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All investigators will follow the applicable conflict of interest policies.

### 6.15 Publication Plan

Study results will be submitted to journals in the fields of ophthalmology, health equity/disparities, and implementation science. Additionally, the PI will submit presentations to national conferences in ophthalmology and implementation science.

# Appendices

| Appendix # | Title | Section | Topic |
|---|---|---|---|

N/A

# List of Tables

N/A

# Literature Review

1. Centers for Disease Control and Prevention. *National diabetes fact sheet: general information and national estimates on diabetes in the United States.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention;2005.
2. Fong DS, Aiello L, Gardner TW, et al. Diabetic retinopathy. *Diabetes Care.* 2003;26(1):226-229.
3. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol.* 1985;103(12):1796-1806.
4. Techniques for scatter and local photocoagulation treatment of diabetic retinopathy: Early Treatment Diabetic Retinopathy Study Report no. 3. The Early Treatment Diabetic Retinopathy Study Research Group. *Int Ophthalmol Clin.* 1987;27(4):254-264.
5. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study Report no. 4. The Early Treatment Diabetic Retinopathy Study Research Group. *Int Ophthalmol Clin.*1987;27(4):265-272.
6. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology.* 1987;94(7):761-774.
7. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology.* 2010;117(6):1064-1077 e1035.
8. Diabetic Retinopathy Study Research Group. Report Number 6. Design, methods, and baseline results. *Invest Ophthalmol Vis Sci.* 1981;21:147-226.
9. Shi Q, Zhao Y, Fonseca V, Krousel-Wood M, Shi L. Racial disparity of eye examinations among the U.S. working-age population with diabetes: 2002-2009. *Diabetes Care.* 2014;37(5):1321-1328.
10. Elam AR, Lee PP. High-Risk Populations for Vision Loss and Eye Care Underutilization: A Review of the Literature and Ideas on Moving Forward. *Survey of Ophthalmology.* 2013;58(4):348-358.
11. Zhang X, Saaddine JB, Chou CF, et al. Prevalence of diabetic retinopathy in the United States, 2005- 2008. *Jama.* 2010;304(6):649-656.
12. Rahmani B, Tielsch JM, Katz J, et al. The cause-specific prevalence of visual impairment in an urban population. The Baltimore Eye Survey. *Ophthalmology.* 1996;103(11):1721-1726.
13. Leske MC, Wu SY, Hyman L, et al. Diabetic retinopathy in a black population: the Barbados Eye Study. *Ophthalmology.* 1999;106(10):1893-1899.

14. Bachmann MO, Eachus J, Hopper CD, et al. Socio-economic inequalities in diabetes complications, control, attitudes and health service use: a cross-sectional study. *Diabet Med.* 2003;20(11):921-929.
15. Harris MI, Klein R, Cowie CC, Rowland M, Byrd-Holt DD. Is the risk of diabetic retinopathy greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites with type 2 diabetes? A U.S. population study. *Diabetes Care.* 1998;21(8):1230-1235.
16. Wong TY KR, Klein BEK. Epidemiology and risk factors of diabetic retinopathy. In: Scott IU FH, Smiddy WE, ed. *Diabetes and Ocular disease: Past, Present, and Future Therapies*. New York: Oxford University Press; 2010:71-89.
17. Keenum Z, McGwin G, Jr., Witherspoon CD, Haller JA, Clark ME, Owsley C. Patients' Adherence to Recommended Follow-up Eye Care After Diabetic Retinopathy Screening in a Publicly Funded County Clinic and Factors Associated With Follow-up Eye Care Use. *JAMA Ophthalmol.* 2016.
18. Lane M, Mathewson PA, Sharma HE, et al. Social deprivation as a risk factor for late presentation of proliferative diabetic retinopathy. *Clinical Ophthalmology.* 2015;9:347-352.
19. Zheng Y, Lamoureux EL, Chiang PC, et al. Language barrier and its relationship to diabetes and diabetic retinopathy. *BMC Public Health.* 2012;12:781.
20. Sequist TD, Cullen T, Bernard K, Shaykevich S, Orav EJ, Ayanian JZ. Trends in quality of care and barriers to improvement in the Indian Health Service. *Journal of General Internal Medicine.* 2011;26(5):480-486.
21. Orton E, Forbes-Haley A, Tunbridge L, Cohen S. Equity of uptake of a diabetic retinopathy screening programme in a geographically and socio-economically diverse population. *Public Health.* 2013;127(9):814-821.
22. Munoz B, O'Leary M, Fonseca-Becker F, et al. Knowledge of diabetic eye disease and vision care guidelines among Hispanic individuals in Baltimore with and without diabetes. *Arch Ophthalmol.* 2008;126(7):968-974.
23. Klein R, Sharrett AR, Klein BE, et al. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes: the atherosclerosis risk in communities study. *Ophthalmology.* 2002;109(7):1225-1234.
24. Klein R, Marino EK, Kuller LH, et al. The relation of atherosclerotic cardiovascular disease to retinopathy in people with diabetes in the Cardiovascular Health Study. *Br J Ophthalmol.* 2002;86(1):84-90.
25. West SK, Munoz B, Klein R, et al. Risk factors for Type II diabetes and diabetic retinopathy in a mexican-american population: Proyecto VER. *Am J Ophthalmol.* 2002;134(3):390-398.
26. Varma R, Mohanty SA, Deneen J, Wu J, Azen SP, Group L. Burden and predictors of undetected eye disease in Mexican-Americans: the Los Angeles Latino Eye Study. *Med Care.* 2008;46(5):497-506.
27. American Academy of Ophthalmology Retina/Vitreous Panel. *Preferred Practice Pattern Guidelines Diabetic Retinopathy.* San Francisco, CA: American Academy of Ophthalmology 2016.
28. Harris Nwanyanwu K, Talwar N, Gardner TW, Wrobel JS, Herman WH, Stein JD. Predicting development of proliferative diabetic retinopathy. *Diabetes Care.* 2013;36(6):1562-1568.
29. Aspelund T, Þórisdóttir Ó, Ólafsdottir E, et al. Individual risk assessment and information technology to optimise screening frequency for diabetic retinopathy. *Diabetologia.* 2011;54(10):2525.
30. Lund SH, Aspelund T, Kirby P, et al. Individualised risk assessment for diabetic retinopathy and optimisation of screening intervals: a scientific approach to reducing healthcare costs. *British Journal of Ophthalmology.* 2016;100(5):683-687.
31. Fairless E NK. Barriers to and facilitators of diabetic retinopathy screening in a high-risk population. Stand strong for science: Stand for strong vision science. Association for Research in Vision and Ophthalmology 2018; Honolulu, Hawaii.

32. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Questionnaire (or Examination Protocol, or Laboratory Protocol). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, [2005-2008][ https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Examination&CycleBeginYear=2005].
33. Cromley EK. GIS and public health. In: McLafferty S, ed. New York: Guilford Press; 2002.
34. Miranda ML, Ferranti J, Strauss B, Neelon B, Califf RM. Geographic Health Information Systems: A Platform To Support The 'Triple Aim'. *Health affairs (Project Hope).* 2013;32(9):1608-1615.
35. Eccles MP, Mittman BS. Welcome to Implementation Science. *Implementation Science.* 2006;1(1):1.
36. Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM. An introduction to implementation science for the non-specialist. *BMC Psychology.* 2015;3(1):32.
37. Wensing M, Oxman A, Baker R, et al. Tailored implementation for chronic diseases (TICD): A project protocol. *Implementation Science.* 2011;6(1):103.
38. Flottorp SA, Oxman AD, Krause J, et al. A checklist for identifying determinants of practice: A systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. *Implementation Science.* 2013;8(1):35.
39. Stein JD, Newman-Casey PA, Kim DD, Nwanyanwu KH, Johnson MW, Hutton DW. Cost-effectiveness of various interventions for newly diagnosed diabetic macular edema. *Ophthalmology.* 2013;120(9):1835-1842.
40. Nwanyanwu KH, Newman-Casey PA, Gardner TW, Lim JI. Beyond HbA1c: Environmental Risk Factors for Diabetic Retinopathy. *J Clin Exp Ophthalmol.* 2015;6(2).
41. Harris Nwanyanwu K, Grossetta Nardini HK, Shaughness G, Nunez-Smith M, Newman-Casey P-A. Systematic review of community-engaged research in ophthalmology. *Expert Review of Ophthalmology.* 2017:1-9.
42. Nwanyanwu K, Warren J. Risk factors associated with complex vitreoretinal surgery for patients with diabetes. Paper presented at: Stand strong for science: Stand for strong vision science. Association for Research in Vision and Ophthalmology2018; Honolulu, Hawaii.
43. Schneider EW, Mruthyunjaya P, Talwar N, Harris Nwanyanwu K, Nan B, Stein JD. Reduced fluorescein angiography and fundus photography use in the management of neovascular macular degeneration and macular edema during the past decade. *Invest Ophthalmol Vis Sci.* 2014;55(1):542-549.
44. Nwanyanwu K, Shaughness G, Nunez-Smith M, Newman-Casey PA. Systematic Review of Community-Engaged Research in Ophthalmology. *Expert Review of Ophthalmology.* 2017.
45. Gross JG. Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. *JAMA: the journal of the American Medical Association.* 2015;314(20):2137-2146.
45. Spanakis EK, Golden SH. Race/ethnic difference in diabetes and diabetic complications. *Current Diabetes Reports.* 2013;13(6):814-823.
46. Bihan H, Laurent S, Sass C, et al. Association among individual deprivation, glycemic control, and diabetes complications: the EPICES score. *Diabetes Care.* 2005;28(11):2680-2685.
47. National Academies of Sciences E, and Medicine. *Making eye health a population health imperative: Vision for tomorrow.* Washington, D.C.: The National Academies Press 2016.
48. Institute NE. *Vision Research: Needs, Gaps, and Opportunities.* National Institutes of Health;2012.

49. National Institute on Minority Health and Health Disparities Research Framework. 2018; https://www.nimhd.nih.gov/about/overview/research-framework.html. Accessed October 3, 2018, 2018
50. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The Diabetic Retinopathy Study Research Group. *Ophthalmology.* 1981;88(7):583-600.
51. Klein RR. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Archives of ophthalmology (1960).* 1984;102(4):520-526.
52. Klein RR. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Archives of ophthalmology (1960).* 1984;102(4):527-532.
53. West SK, Klein R, Rodriguez J, et al. Diabetes and diabetic retinopathy in a Mexican-American population: Proyecto VER. *Diabetes Care.* 2001;24(7):1204-1209.
54. Mitchell PP. Prevalence of diabetic retinopathy in an older community. The Blue Mountains Eye Study. *Ophthalmology (Rochester, Minn.).* 1998;105(3):406-411.
55. Roy MSM. Diabetic retinopathy in African Americans with type 1 diabetes: The New Jersey 725: I. Methodology, population, frequency of retinopathy, and visual impairment. *Archives of ophthalmology (1960).* 2000;118(1):97-104.
56. Klein RR. The Beaver Dam Eye Study. Retinopathy in adults with newly discovered and previously diagnosed diabetes mellitus. *Ophthalmology (Rochester, Minn.).* 1992;99(1):58-62.
57. Tielsch JMJ. Blindness and visual impairment in an American urban population. The Baltimore Eye Survey. *Archives of ophthalmology (1960).* 1990;108(2):286-290.
58. The Diabetes Control and Complications Trial Research Group. The Relationship of Glycemic Exposure (HbA1c) to the Risk of Development and Progression of Retinopathy in the Diabetes Control and Complications Trial. *Diabetes.* 1995;44(8):968-983.
59. Jandorf L, Gutierrez Y, Lopez J, Christie J, Itzkowitz SH. Use of a patient navigator to increase colorectal cancer screening in an urban neighborhood health clinic. *Journal of Urban Health: Bulletin of the New York Academy of Medicine.* 2005;82(2):216-224.
60. Phillips CE, Rothstein JD, Beaver K, Sherman BJ, Freund KM, Battaglia TA. Patient Navigation to Increase Mammography Screening Among Inner City Women. *Journal of General Internal Medicine.* 2011;26(2):123-129.
61. Ahmed NU, Haber G, Semenya KA, Hargreaves MK. Randomized Controlled Trial of Mammography Intervention in Insured Very Low–Income Women. *Cancer Epidemiology Biomarkers & Prevention.* 2010;19(7):1790-1798.
62. Paskett E, Tatum C, Rushing J, et al. Randomized Trial of an Intervention to Improve Mammography Utilization Among a Triracial Rural Population of Women. *JNCI: Journal of the National Cancer Institute.* 2006;98(17):1226-1237.
63. West DS, Greene P, Pulley L, et al. Stepped-Care, Community Clinic Interventions to Promote Mammography Use among Low-Income Rural African American Women. *Health Education & Behavior.* 2004;31(4_suppl):29S-44S.
64. Weber BE, Reilly BM. Enhancing mammography use in the inner city: A randomized trial of intensive case management. *Archives of Internal Medicine.* 1997;157(20):2345-2349.
65. Percac-Lima S, Grant RW, Green AR, et al. A Culturally Tailored Navigator Program for Colorectal Cancer Screening in a Community Health Center: A Randomized, Controlled Trial. *Journal of General Internal Medicine.* 2009;24(2):211-217.
66. Christie Jennifer IS, Lihau-Nkanza I, Castillo A, Redd W, Jandorf L. A randomized controlled trial using patient navigation to increase colonoscopy screening among low-income minorities. *Journal of the National Medical Association.* 2008;100(3):278-284.
67. Lasser KE, Murillo J, Lisboa S, et al. Colorectal cancer screening among ethnically diverse, low-income patients: A randomized controlled trial. *Archives of Internal Medicine.* 2011;171(10):906-912.

68. DeGroff A, Schroy PC, III, Morrissey KG, et al. Patient Navigation for Colonoscopy Completion: Results of an RCT. *American Journal of Preventive Medicine.* 2017;53(3):363-372.
69. Dietrich AJ, Tobin JN, Cassells A, et al. Telephone care management to improve cancer screening among low-income women: A randomized, controlled trial. *Annals of Internal Medicine.* 2006;144(8):563-571.
70. Taylor VM, Hislop TG, Jackson JC, et al. A Randomized Controlled Trial of Interventions to Promote Cervical Cancer Screening Among Chinese Women in North America. *Journal of the National Cancer Institute.* 2002;94(9):670-677.
71. Taylor VM, Jackson JC, Yasui Y, et al. Evaluation of a Cervical Cancer Control Intervention Using Lay Health Workers for Vietnamese American Women. *American Journal of Public Health.* 2010;100(10):1924-1929.
72. Marshall JK, Mbah OM, Ford JG, et al. Effect of Patient Navigation on Breast Cancer Screening Among African American Medicare Beneficiaries: A Randomized Controlled Trial. *Journal of General Internal Medicine.* 2016;31(1):68-76.
73. Basch CE, Wolf RL, Brouse CH, et al. Telephone Outreach to Increase Colorectal Cancer Screening in an Urban Minority Population. *American Journal of Public Health.* 2006;96(12):2246-2253.
74. Coronado GD, Golovaty I, Longton G, Levy L, Jimenez R. Effectiveness of a clinic-based colorectal cancer screening promotion program for underserved Hispanics. *Cancer.* 2011;117(8):1745-1754.
75. Myers RE, Sifri R, Daskalakis C, et al. Increasing Colon Cancer Screening in Primary Care Among African Americans. *JNCI: Journal of the National Cancer Institute.* 2014;106(12): dju344-dju344.
76. Enard KR, Nevarez L, Hernandez M, et al. Patient Navigation to Increase Colorectal Cancer Screening among Latino Medicare Enrollees: A Randomized Controlled Trial. *Cancer causes & control: CCC.* 2015;26(9):1351-1359.
77. Cole H, Thompson HS, White M, et al. Community-Based, Preclinical Patient Navigation for Colorectal Cancer Screening Among Older Black Men Recruited From Barbershops: The MISTER B Trial. *American Journal of Public Health.* 2017;107(9):1433-1440.
78. Braun KL, Thomas WL, Domingo J-LB, et al. Reducing Cancer Screening Disparities in Medicare Beneficiaries Through Cancer Patient Navigation. *Journal of the American Geriatrics Society.* 2015;63(2):365-370.
79. Rahm AK, Sukhanova A, Ellis J, Mouchawar J. Increasing utilization of cancer genetic counseling services using a patient navigator model. *Journal of genetic counseling.* 2007;16(2):171-177.
80. Prezio EA, Cheng D, Balasubramanian BA, Shuval K, Kendzor DE, Culica D. Community Diabetes Education (CoDE) for uninsured Mexican Americans: A randomized controlled trial of a culturally tailored diabetes education and management program led by a community health worker. *Diabetes Research and Clinical Practice.* 2013;100(1):19-28.
81. Thom DH, Ghorob A, Hessler D, De Vore D, Chen E, Bodenheimer TA. Impact of Peer Health Coaching on Glycemic Control in Low-Income Patients With Diabetes: A Randomized Controlled Trial. *The Annals of Family Medicine.* 2013;11(2):137-144.
82. Spencer MS, Rosland A-M, Kieffer EC, et al. Effectiveness of a Community Health Worker Intervention Among African American and Latino Adults With Type 2 Diabetes: A Randomized Controlled Trial. *American journal of public health.* 2011;101(12):2253-2260.
83. Svoren BM, Butler D, Levine B-S, Anderson BJ, Laffel LMB. Reducing Acute Adverse Outcomes in Youths With Type 1 Diabetes: A Randomized, Controlled Trial. *Pediatrics.* 2003;112(4):914-922.
84. Laffel LM, Brackett J, Ho J, Anderson BJ. Changing the process of diabetes care improves metabolic outcomes and reduces hospitalizations. *Quality management in health care.* 1998;6(4):53-62.

85. Corkery E, Palmer C, Schechter CB, Frisher L, Roman SH. Effect of a bicultural community health worker on completion of diabetes education in a Hispanic population. *Diabetes care.*20(3):254-257.
86. Loskutova NY, Tsai AG, Fisher EB, LaCruz DM, Cherrington AL, Harrington TM, Turner TJ, Pace WD. Patient Navigators Connecting Patients to Community Resources to Improve Diabetes Outcomes. *Journal of the American Board of Family Medicine.*29(1):78-89.
87. do Valle Nascimento TMR, Resnicow K, Nery M, et al. A pilot study of a Community Health Agent-led type 2 diabetes self-management program using Motivational Interviewing-based approaches in a public primary care center in São Paulo, Brazil. *BMC Health Services Research.* 2017;17(1):32.
88. Rubenstein LV, Pugh J. Strategies for Promoting Organizational and Practice Change by Advancing Implementation Research. *Journal of General Internal Medicine.* 2006;21(Suppl 2): S58-S64.
89. Colquhoun HL, Squires JE, Kolehmainen N, Fraser C, Grimshaw JM. Methods for designing interventions to change healthcare professionals' behaviour: a systematic review. *Implementation Science.* 2017;12(1):30.
90. Wensing M. The Tailored Implementation in Chronic Diseases (TICD) project: introduction and main findings. *Implementation Science.* 2017;12(1):5.
91. Jäger C, Freund T, Steinhäuser J, et al. Tailored Implementation for Chronic Diseases (TICD): a protocol for process evaluation in cluster randomized controlled trials in five European countries. *Trials.* 2014;15(1):87.
92. Aakhus E, Granlund I, Odgaard-Jensen J, Wensing M, Oxman AD, Flottorp SA. Tailored interventions to implement recommendations for elderly patients with depression in primary care: a study protocol for a pragmatic cluster randomised controlled trial. *Trials.* 2014;15(1):16.
93. Campbell W, Camden C, Missiuna C. Reflections on Using a Community-Based and Multisystem Approach to Transforming School-Based Intervention for Children with Developmental Motor Disorders. *Current Developmental Disorders Reports.* 2016;3(2):129-137.
94. Bos JM, Natsch S, van den Bemt PMLA, et al. A multifaceted intervention to reduce guideline non- adherence among prescribing physicians in Dutch hospitals. *International Journal of Clinical Pharmacy.* 2017;39(6):1211-1219.
95. Backman R, Foy R, Michael BD, Defres S, Kneen R, Solomon T. The development of an intervention to promote adherence to national guidelines for suspected viral encephalitis. *Implementation Science.* 2015;10(1):37.
96. Zhang XX. Diabetic retinopathy, dilated eye examination, and eye care education among African Americans, 1997 and 2004. *J Natl Med Assoc.* 2009;101(10):1015-1021.
97. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, [2005-2008][ https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Examination&CycleBeginYear=2005].
98. Duncan GEGE. Prevalence of diabetes and impaired fasting glucose levels among US adolescents: National Health and Nutrition Examination Survey, 1999-2002. *Archives of pediatrics & adolescent medicine.* 2006;160(5):523-528.
99. Demmer RT, Zuk AM, Rosenbaum M, Desvarieux M. Prevalence of diagnosed and undiagnosed type 2 diabetes mellitus among US adolescents: results from the continuous NHANES, 1999-2010. *Am J Epidemiol.* 2013;178(7):1106-1113.
100. Messer LCLC. The development of a standardized neighborhood deprivation index. *Journal of urban health.* 2006;83(6):1041-1062.

101. Scanlon PH, Carter SC, Foy C, Husband RF, Abbas J, Bachmann MO. Diabetic retinopathy and socioeconomic deprivation in Gloucestershire. *Journal of Medical Screening.* 2008;15(3):118-121.
102. Ahmed OM AD, Juthani P, Nwanyanwu K. A Needs Assessment of Video-based Diabetic Retinopathy Education Among Patients and Physicians. American Medical Association Research Symposium 2018; National Harbor, Maryland.
103. Nilsen P. Making sense of implementation theories, models and frameworks. *Implementation Science.* 2015;10(1):53.
104. Wilkinson CP, Ferris FL, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology.* 2003;110(9):1677-1682.
105. Arozullah AM, Yarnold PR, Bennett CL, et al. Development and Validation of a Short-Form, Rapid Estimate of Adult Literacy in Medicine. *Med Care.* 2007;45(11):1026-1033.
106. Kolko J. 'Normal America' is not a small town of white people. *Five Thirty Eight*. Internet 2016 [https://fivethirtyeight.com/features/normal-america-is-not-a-small-town-of-white-people/].
107. Abraham M, Buchanan M. *Greater New Haven Community Index.* New Haven, Connecticut: DataHaven; 2016.
109. Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: a confidence interval approach. Journal of Clinical Epidemiology. 2013;66(2):197-201.
110. Hipwell AE, Sturt J, Lindenmeyer A, et al. Attitudes, access and anguish: a qualitative interview study of staff and patients' experiences of diabetic retinopathy screening. BMJ Open. 2014;4(12): e005498.
111. Alexander RL, Jr., Miller NA, Cotch MF, Janiszewski R. Factors that influence the receipt of eye care. Am J Health Behav. 2008;32(5):547-556.
112. Owsley C, McGwin G, Scilley K, et al. Perceived barriers to care and attitudes about vision and eye care: focus groups with older African Americans and eye care providers. Invest Ophthalmol Vis Sci. 2006;47(7):2797-2802.
113. Lindenmeyer A, Sturt JA, Hipwell A, et al. Influence of primary care practices on patients' uptake of diabetic retinopathy screening: a qualitative case study. Br J Gen Pract. 2014;64(625): e484-492.
114. Hartnett ME, Key IJ, Loyacano NM, Horswell RL, Desalvo KB. Perceived barriers to diabetic eye care: qualitative study of patients and physicians. Arch Ophthalmol. 2005;123(3):387-391.
115. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. Epidemiology (Cambridge, Mass.).2010;21(1):128-138.