This document is provided as a sample application. Some pages and text have been redacted.

PI: **Baxter, Sally Liu**	Title: Multi-modal Health Information Technology Innovations for Precision Management of Glaucoma	
Received: 09/13/2019	Opportunity: RFA-RM-19-008 Clinical Trial:Optional	Council: 05/2020
Competition ID: FORMS-E	FOA Title: NIH Directors Early Independence Awards (DP5 Clinical Trial Optional)	
1DP5OD029610-01	Dual: RM,DE	Accession Number: 4348115
IPF: 577507	Organization: UNIVERSITY OF CALIFORNIA, SAN DIEGO	
Former Number:	Department: Ophthalmology	
IRG/SRG: ZRG1 PSE-H (70)R	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 250,000 Year 2: 250,000 Year 3: 250,000 Year 4: 250,000 Year 5: 250,000	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N HFT: N	New Investigator: Y Early Stage Investigator: Y
Senior/Key Personnel:	*Organization:*	*Role Category:*
Sally Baxter	The Regents of the Univ. of Calif., U.C. San Diego	PD/PI

Reference Letters

[redacted]

Additions for Review

Accepted Publication Newly accepted publications

OMB Number: 4040-0001
Expiration Date: 10/31/2019

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

○ Pre-application ● Application ○ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

2. DATE SUBMITTED

Application Identifier
00021996

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational DUNS*: [redacted]

Legal Name*: The Regents of the Univ. of Calif., U.C. San Diego
Department: Health Sciences SPO
Division: [redacted]
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]

Person to be contacted on matters involving this application
Prefix: [redacted] First Name*: [redacted] Middle Name: Last Name*: [redacted] Suffix:
Position/Title: Grant Analyst
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email: [redacted]

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** [redacted]

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ○ Women Owned ○ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ○ Resubmission
○ Renewal ○ Continuation ○ Revision

If Revision, mark appropriate box(es).
○ A. Increase Award ○ B. Decrease Award ○ C. Increase Duration
○ D. Decrease Duration ○ E. Other *(specify)* :

Is this application being submitted to other agencies?* ○Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Multi-modal Health Information Technology Innovations for Precision Management of Glaucoma

12. PROPOSED PROJECT
Start Date*: 09/01/2020
Ending Date*: 08/31/2025

13. CONGRESSIONAL DISTRICTS OF APPLICANT
CA-049

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Sally Middle Name: Liu Last Name*: Baxter Suffix:
Position/Title: Postdoctoral Fellow
Organization Name*: The Regents of the Univ. of Calif., U.C. San Diego
Department: [redacted]
Division: [redacted]
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email*: [redacted]

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested* [redacted]
b. Total Non-Federal Funds* [redacted]
c. Total Federal & Non-Federal Funds* [redacted]
d. Estimated Program Income* [redacted]

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: [redacted] Middle Name: Last Name*: [redacted] Suffix:
Position/Title*: Grant Analyst
Organization Name*: The Regents of the Univ. of Calif., U.C. San Diego
Department: [redacted]
Division: [redacted]
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email*: [redacted]

Signature of Authorized Representative* [redacted]

Date Signed* [redacted]

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:CoverLetter_Baxter_earlyindep.pdf

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ● **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number [redacted]

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	project_summary_abstract.pdf
8. Project Narrative*	project_narrative.pdf
9. Bibliography & References Cited	bibliography.pdf
10.Facilities & Other Resources	Facilities_Resources_v2.pdf
11.Equipment	Equipment.pdf

Funding Opportunity Number: RFA-RM-19-008. Received Date: 2019-09-13T15:56:35.000-04:00

PROJECT SUMMARY/ABSTRACT

Glaucoma is the world's leading cause of irreversible blindness and will affect >110 million people by 2040. Early detection and treatment are critical, as symptoms typically do not present until the disease is advanced. A data-driven precision medicine approach is needed to better identify individuals who are at greatest risk of developing the disease and who are at greatest risk of progressing quickly to vision loss. While there has been considerable progress in eye imaging and testing to improve glaucoma monitoring, precision management of glaucoma is incomplete without accounting for patients' co-existing systemic conditions, concurrent systemic medications and treatments, and adherence with prescribed glaucoma treatment. Understanding how systemic conditions, and specifically vascular conditions such as hypertension, impact glaucoma presents growing public health importance given the increasing co-morbidities facing aging populations. Preliminary studies have demonstrated the predictive value of systemic data, even without ophthalmic endpoints. Similarly, measuring medication adherence is important for guiding patient counseling and engagement and avoiding downstream interventions such as surgeries, which carry high cost and morbidity. These factors are important for providing a more comprehensive perspective of glaucoma management and for improving patient outcomes, yet they are relatively understudied.

I propose applying multi-modal advancements in health information technology (IT) to address these gaps and achieve the following specific aims: (1) Develop machine learning-based predictive models classifying patients at risk for glaucoma progression using systemic electronic health record (EHR) data from a diverse nationwide patient cohort; (2) evaluate how integrating blood pressure (BP) data from novel smartwatch-based home BP monitors enhance predictive models for risk stratification in glaucoma, and (3) measure glaucoma medication adherence using innovative flexible electronic sensors to validate their use for future interventions aimed at improving adherence and clinical outcomes in glaucoma. These studies would leverage state-of-the-art methods in big-data predictive modeling as well as cutting-edge advancements in sensor technologies. This multi-faceted approach will build a foundation for a health IT framework geared toward improving risk stratification and generating novel therapeutic targets for glaucoma patients.

PROJECT NARRATIVE

A precision medicine approach is critical for early detection and treatment of glaucoma, an insidious chronic eye disease that can lead to blindness and severely decreased quality of life. The relationship between systemic conditions and treatments with glaucoma progression, as well as methods for monitoring and promoting glaucoma medication adherence, represent areas of glaucoma management that are not well-understood and are thus critical opportunities for technology-driven interventions. This study proposes the development and application of multi-modal health information technology innovations – such as machine learning-based predictive modeling, massive electronic datasets, wearable devices, and flexible sensor electronics – to enhance understanding of glaucoma pathophysiology and identify new potential therapeutic strategies.

FACILITIES & OTHER RESOURCES

1. Position Details

After completion of Dr. Sally Baxter's current postdoctoral fellowship, she will be appointed as an Assistant Professor of Ophthalmology (primary appointment) and Biomedical Informatics (secondary appointment). This will be a tenure-track equivalent position. Her appointment will not be contingent upon receipt of the Early Independence Award. To ensure independence, not only will she be given dedicated workspace and granted extensive support from both departments, she will also be guaranteed protected time for research by limiting administrative and service commitments. Her clinical activities will allow her to maintain clinical and surgical competency, and notably will not detract from her research efforts. By limiting other commitments, she will devote at least 9.6 person-months each year to the Early Independence Award in years 1-2 of the project period, and equivalent effort to research in general in years 3-5. **This protected time will be ensured by department chairs in both [redacted] and [redacted].**

Dr. Baxter's appointment is based on the following criteria:

- Demonstration of academic and clinical excellence
- Appropriate medical doctorate training and completion of post-graduate residency training and postdoctoral fellowship training
- Board-eligible status
- Contribution to faculty diversity as a woman of color, and
- Potential for ongoing academic productivity and impact

Her position will be administered through the UCSD Department of Ophthalmology and the UCSD Health Department of Biomedical Informatics (DBMI), both of which fall within the UCSD School of Medicine and within the broader UCSD Health Sciences. Appointments within both ophthalmology and biomedical informatics will promote her ability to conduct her research and interact with wide range of investigators across multiple fields.

The scientific and intellectual environment at UCSD is outstanding for Dr. Baxter's development into an independent investigator conducting translational vision research using biomedical informatics approaches. UCSD offers an incredible range of facilities and resources directly related to her proposed research and areas of study which will contribute to her success.

UCSD is one of the nation's top-ranked public universities with an intensive focus on research and innovation. It is home to an expansive array of departments, institutes, and programs in the Health Sciences, as well as offering strengths in computer science, data science, and engineering, and is thus uniquely qualified to support the proposed study. Though founded less than 60 years ago, its emphasis on interdisciplinary collaboration and innovation has allowed UCSD to undergo a remarkable rise to prominence, achieving >$1 billion in total research funding and Top 10 Federal Funding status, Top 3 NIH funding per faculty member, >160 faculty and emeritus memberships in one or more of the National Academies, and ranked in the top 15 best universities in the world by the Center for World Class Universities. UCSD features a highly-ranked School of Medicine in addition to top-ranked graduate programs across multiple fields of study (biological sciences, neuroscience, bioengineering as a few examples). With this vibrant community, UCSD provides a unique environment for young clinician-scientists to develop outstanding research programs and has a long track record of providing multi-institutional and multi-disciplinary training opportunities, in line with the proposed training plan in this application.

The UCSD Viterbi Family Department of Ophthalmology has long demonstrated exceptional research prowess and is highly ranked for both total National Eye Institute (NEI) funding as well as NEI funding per faculty member. Currently, the full-time faculty includes 24 clinician-scientists/clinicians and 13 PhD scientists. The department is committed to continued growth of its vision research program and encourages cross-disciplinary collaboration both within and outside UCSD. Some of the developments in the last 5 years that illustrate both UCSD's and the department's commitment to research and research training include the following: recruitment of both established/senior research investigators ([redacted]) and early career investigators ([redacted])

[redacted]), new offices at the Shiley Eye Institute/Hamilton Glaucoma Center complex, additional laboratory space at the Medical Teaching Facility/Biomedical Science Building complex for use by clinician-scientists, dedicated grants/administrative staff time, new pilot research funding to Department of Ophthalmology investigators [redacted]) to acquire preliminary data necessary to compete for NEI RO1 grants, [redacted] commitment to increase Department of Ophthalmology research infrastructure through tissue banking services and an ocular Biobank, and a [redacted] commitment to develop a Research Computing Unit for the UCSD Shiley Eye Institute Research Computing Center and Storage Cloud. With a recent [redacted] lead donation from [redacted], plans are underway to construct the Viterbi Family Vision Research Center, a state-of-the-art research facility anticipated to encompass 70,000-80,000 square feet to further enhance research capacity and interdisciplinary collaborations.

As another demonstration of its research strengths, the UCSD Viterbi Family Department is the recipient of an **NIH P30 Center Core Grant for Vision Research,** providing [redacted] in annual funding for modules in: 1) Vision Biostatistics, 2) Animal Structure and Function, 3) Computational Ophthalmology, and 4) Tissue Processing and Confocal Microscopy. Dr. Baxter has access to all the core facilities and resources, although her proposed research will primarily interact with the Biostatistics module. This module provides statistical analyses and consultation to investigators, and provides a full-time biostatistician ([redacted]) to ophthalmology investigators to advise on analysis strategies and implement sophisticated statistical techniques. Dr. Baxter has already begun collaborating with [redacted], who previously worked in the UCSD Altman Clinical and Translational Research Institute (ACTRI) under [redacted], prior to working full-time for ophthalmology. Thus, by receiving mentorship and guidance from [redacted] as well as by actively collaborating with [redacted], Dr. Baxter has assembled a capable team of statistical experts to ensure the success of the proposed research and to advance her own statistical expertise.

UCSD is also one of a select few universities nationwide to have a **K12 institutional training grant from the National Eye Institute**. The PI of the K12 program, [redacted] is one of Dr. Baxter's mentors and thus offers exceptional expertise in guiding young investigators. The K12 program also hosts several structured department-wide activities, including monthly meetings of K candidates, recipients and faculty, in which Dr. Baxter participates. A variety of educational and training activities are also hosted by the department to encourage interaction among investigators, clinicians, and visiting scholars from other institutions. Dr. Baxter will continue to participate in these programs to enhance her career development:

- ***Visiting Scientists-Grand Rounds series:*** As part of the departmental grand rounds programming, world-class physician-scientists are invited to UCSD every month throughout the academic year to give seminars in their area of interest and meet with faculty and trainees. Private meetings are arranged between these visiting professors and faculty, which represents an opportunity for Dr. Baxter to expand her network and potentially forge new collaborations.
- ***Shiley Eye Institute Research Seminar****:* K award recipients, early stage investigators, and postdoctoral fellows from the Department of Ophthalmology as well as the laboratories of the Research Faculty will attend and present their research in progress. Faculty will attend and present monthly at the seminars. Moreover, Departmental fellows working in laboratories throughout the School of Medicine will be invited to present their results and build collaborative networks among the Scholars and the broader research community.

The UCSD Hamilton Glaucoma Center is a free-standing facility dedicated to research in glaucoma and the first of its kind in the world. It serves as a hub for laboratory, translational, and clinical research in glaucoma, with 8 Clinical Research Coordinators who assist with clinical trials sponsored by the NEI and other funding sources. Two dedicated database managers oversee a clinical research database that includes the Diagnostic Innovations in Glaucoma Study (DIGS, funded since 1990) and ADAGES (African Ancestry Glaucoma Evaluation Study, funded since 2003). Hamilton features perhaps the world's most comprehensive supply of tools for optic nerve and anterior segment imaging and serves as a reading center for imaging instruments, photography, and visual fields for national and international multi-center studies. Also included in the facility is a 24-hour sleep laboratory, Laboratory for Optic Nerve Biology, and Laboratory for Glaucoma Neurobiology. As

Dr. Baxter's proposed research is focused on glaucoma progression, she will have access to all of the resources and personnel at the UCSD Hamilton Glaucoma Center to advance her research.

The UCSD Health System Department of Biomedical Informatics (DBMI) was founded in 2009 and has quickly become a leader in the field. It serves as a hub for biomedical informatics research and is responsible for the clinical research informatics infrastructure at the Altman Clinical and Translational Research Institute (ACTRI), including applications for managing clinical research data and the bio-sample repository. It is the only BMI division in the entire UC system to have dedicated tenure-line state-funded positions and has recruited an array of faculty with a broad range of expertise, including predictive modeling, natural language processing, imaging, implementation science, human computer interaction, clinical decision support and evaluation methods. Currently it is composed of 20 members trained in health sciences (medicine, genomics, biology, and nursing), computer science/engineering, and/or biomedical informatics, 42 staff, 7 postdocs, and 14 PhD students. Its physical space includes office space in the Biomedical Research Facility II (BRF2) building adjacent to the UCSD School of Medicine, the ACTRI on the Health Sciences campus, and a cluster of buildings on the main UCSD campus dedicated to study visits for the All of Us Research Program.

DBMI has a history of hosting large projects such as iDASH (integrating Data for Analysis, 'anonymization,' and SHaring), one of the NIH-funded National Centers for Biomedical Computing (NCBC), and currently leads several others such as pSCANNER (patient-centered SCAlable National Network for Effectiveness Research), a PCORI-funded clinical data research network covering over 21 million patients and 10 health systems, and the NIH-funded California Precision Medicine Consortium. In less than 10 years, [redacted] has secured over [redacted] in grant funding for DBMI and its associated projects.

Additionally, the DBMI has a central role in clinical and research informatics at the UCSD Health System, operating across multiple departments and organized research units within the Schools of Medicine, Pharmacy, and Engineering/Computer Science. It is integrated with the Information Services of the UCSD Health System via common faculty, including UCSD's Chief Information Officer and all of UCSD's Chief Medical Information Officers. DBMI is also charged with the development, refinement, and expansion of the Clinical Data Warehouse for Research, a derivative of the Electronic Health Record (EHR) system, as well as other data repositories. This facilitates seamless integration of research and clinical information technology activities and provides a path for Dr. Baxter to implement the findings of her predictive models into informatics interventions for real-world clinical deployment.

In terms of computational resources, DBMI offers enhanced resources that will support Dr. Baxter's proposed research. UCSD is served by a 10 Gigabit network connecting campus computers and the Health System, as well as to several other institutions nationally. DBMI also manages a private cloud facility compliant with the Health Insurance Portability and Accountability Act (HIPAA) and the Federal Information Security Management Act (FISM) with >1000 cores and 2 PB of tiered storage. Dr. Baxter has access to this server for her research.

DBMI is heavily engaged in education and training. It plays a key role in (1) doctoral programs in Bioinformatics/Biomedical Informatics (http://bioinformatics.ucsd.edu), (2) the Computer Science and Engineering doctoral program, (3) the Cognitive Science doctoral program, (4) a new Master's program in Data Science, and (5) a Master's in Advanced Studies in Clinical Research program, which trains clinical researchers and medical students. The DBMI has been awarded a T15 training grant in biomedical informatics from the National Library of Medicine. Additionally, DBMI funds other long-term trainees through research grants and over a dozen summer interns every year, with a strong emphasis on the recruiting trainees from underrepresented groups such as women, minorities, and economically disadvantaged populations. As one of the NLM-funded postdoctoral fellows, Dr. Baxter has been well-integrated into the DBMI education and training community. She will continue collaborating with the training program as faculty, and the training programs will also serve as a source of trainees to help her with projects and become integrated into her research program.

The **UCSD Altman Clinical and Translational Research Institute (ACTRI)** is an organized research unit based at UCSD to provide researchers with education, resources, and collaborations to accelerate translational research. It is based upon a partnership between UCSD and neighboring institutions in San Diego dedicated to improving health and serves as a central hub for clinical research services. These institutions

UCSD offers the **Clinical Research Enhancement through Supplemental Training (CREST) Program** to provide a structured training program for faculty interested in conducting clinical research. The program includes a broad-based curriculum encompassing all major areas of clinical research, including principles of epidemiology, biostatistics, patient-oriented research, health services/outcomes research, data management/informatics, and professional development seminars encompassing grant writing, scientific communication, research management and time management. By participating in CREST courses, Dr. Baxter will not only gain key skills pertaining to her research, but she will also be able to engage in frequent intellectual interactions with fellow early career clinician-investigators in a like-minded community of peers.

Having completed her residency and fellowship training in Ophthalmology and DBMI, Dr. Baxter is already well-acquainted with leadership and faculty in both departments. However, there are multiple mechanisms by which she will continue integrating into the community and institutional culture once she transitions to faculty. At the UCSD Shiley Eye Institute, she participates in group meetings of early-stage faculty funded on K12, K08, or K23 career development awards, where junior faculty meet with senior leaders and mentors to discuss proposals, project ideas, and provide updates on research projects and receive feedback. She also attends the UCSD Shiley Eye Institute Vision Research Lectures, Grand Rounds, and Visiting Professor Lecture Series. On the informatics side, Dr. Baxter attends DBMI Town Hall meetings, the DBMI Guest Lecture Series, Biomedical Informatics journal clubs, and the MED 262: Current Trends in Biomedical Informatics seminar series. In both departments, these academic forums provide venues for formative engagement and discourse with other faculty and trainees. Dr. Baxter has also been invited to social events and celebrations for both departments to facilitate informal interactions. In the broader UCSD community, Dr. Baxter will participate in the National Center of Leadership in Academic Medicine (NCLAM) program, a structured and mentored professional development program for junior faculty at UCSD, consisting of a series of workshops encompassing teaching, research, professional development, and leadership training.

UCSD expects to retain Dr. Baxter at the end of the funding period of the NIH Director's Early Independence Award and will support her efforts to obtain continued independent research funding. If she is unable to secure continued independent research funding by the end of the award period, Ophthalmology and DBMI will provide bridge funding until she is able to do so.

2. Institutional Resources Commitment

Office Space: Dr. Baxter will be given workspace for herself and her research team on the second floor of the UCSD Shiley Eye Institute, which is one of the primary locations of administrative and research activities of the UCSD Department of Ophthalmology. The space consists of a main office (Shiley Room E215), measuring 195 square feet, as well as an adjoining anteroom office (Shiley Room E214), measuring 110 square feet. The two rooms will allow workspace for Dr. Baxter's research team as well as individual enclosed space for herself. The workspace will be furnished with desks, chairs, and storage units, and can easily accommodate 4-6 computer workstations and a printing station. Each workstation will be equipped with the latest version of Microsoft Windows, Internet Explorer, Google Chrome, R Studio, Zotero, Adobe Acrobat 9 Professional, Zoom (for teleconferencing capabilities) and other supporting software, and high-definition widescreen monitors. Several bookshelves and cabinets will also be provided for storing research-related documents, binders, and other supplies. The workspace will be within easy access of the ophthalmology clinics (1st floor of the UCSD Shiley Eye Institute) as well as the UCSD Hamilton Glaucoma Center. The UCSD Hamilton Glaucoma Center is a free-standing glaucoma research facility that is adjacent to the UCSD Shiley Eye Institute and directly accessible on the 2nd floor via a pedestrian bridge walkway. Dr. Baxter will have access to the UCSD Hamilton Glaucoma Center for patient-oriented clinical research activities. The Hamilton Glaucoma Center houses an array of ophthalmic imaging equipment, several examination rooms dedicated to clinical research visits, and a team of clinical research support staff. She will also have access to the UCSD Hamilton Glaucoma Center Conference Room and the UCSD Shiley Eye Institute Library for organizing conferences or team/group meetings.

Computational Environment: UCSD has a plethora of computer workstations for faculty use. All computer workstations in the Department of Ophthalmology as well as in DBMI are with up-to-date versions of Windows,

EQUIPMENT

Dr. Sally Baxter has the necessary equipment to complete the study aims. These include equipment for measuring clinical ophthalmic outcomes, blood pressure monitoring, glaucoma medication adherence monitoring, and computational resources for predictive modeling.

Equipment for measuring ophthalmic outcomes
Shiley Eye Institute, UCSD and Hamilton Glaucoma Center, UCSD

- Goldmann applanation tonometer to measure intraocular pressure
- iCare tonometer to measure intraocular pressure
- Pachymeter to measure corneal thickness
- 2 Humphrey Visual Field Analyzers (Carl Zeiss Meditec)
- Spectralis spectral domain OCT (Heidelberg Engineering GmbH)
- OCT Angiography and spectral domain OCT (Avanti Angiovue, Optovue Inc.)

Equipment for measuring blood pressure
Shiley Eye Institute, UCSD and Hamilton Glaucoma Center, UCSD

- Blood pressure monitors (Omron HeartGuide, Omron Inc.)

Equipment for medication adherence sensors (for complete list, see: http://nano3.calit2.net/equipment/index.php)
Powell-Focht Bioengineering Hall, UCSD

- Bio-Rad MRC-1024UV confocal microscope, for characterizing the mechanical attachment of the flexible electronic devices with soft materials such as eyedrop medication labels
- Atomic Force Microscope (AFM), for characterizing surface properties of flexible electronics

Nano3 clean room facility, UCSD

- PDMS clean space with Thinky Mixer, Laurel Spin Coater, scale, vacuum desiccator and oven
- UVO cleaner, for material surface processing
- Oxford Plasmalab 100 RIE/ICP and 80 RIE, for dry etching
- AJA RF and DC Sputter Deposition Tools, for thin-film deposition
- Temescal BJD 1800 Ebeam Evaporator and Denton 502A Ebeam Evaporator, for metallic thin film depositing
- Oxford Plasmalab PECVD, for semi-conductor material depositing
- Agilent B1500 Semiconductor Device Analyzer, for device characterization
- Karl Suss MA6 and MJB3 Mask Aligners, for photolithography

Equipment for predictive modeling
Altman Clinical and Translational Research Institute, UCSD and Shiley Eye Institute, UCSD

- Computer workstations equipped with RStudio, Python, Jupyter notebooks, Microsoft Office, Adobe Acrobat 9 Professional, reference management software, and videoconferencing capabilities located at the UCSD Altman Clinical and Translational Research Institute (ACTRI) and the Shiley Eye Institute.
- All computer workstations are connected to the UCSD network, have high-speed Internet connectivity, and full technical support from the UCSD Information Technology Services.

- Server hosted by the UCSD Health Department of Biomedical Informatics which provides a HIPAA-compliant cloud environment for research through iDASH (integrating Data for Analysis, 'anonymization,' and SHaring), which includes over 1000 cores and over 2PB of a hybrid SSD/HDD storage backend
- Additional high-performance computing resources are also available at the San Diego Supercomputer Center

General Workspace Equipment
Altman Clinical and Translational Research Institute, UCSD and Shiley Eye Institute, UCSD

- Office and desk space for Dr. Baxter
- Computer workstations (see above section for details)
- Widescreen computer monitors
- Hewlett Packard LaserJet 4730 Multifunction Printer with printer, photocopy, and fax capabilities (ACTRI office)
- Hewlett Packard LaserJet P2055dn printer (Shiley Eye Institute office)
- Telephones
- Whiteboards
- Office supplies

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Sally Middle Name Liu Last Name*: Baxter Suffix:

Position/Title*: Postdoctoral Fellow
Organization Name*: The Regents of the Univ. of Calif., U.C. San Diego
Department: [redacted]
Division:
Street1*:
Street2:
City*:
County:
State*:
Province:
Country*:
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number:

E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: MD,MSc,BS Degree Year: 2014,2010,2009

Attach Biographical Sketch*: File Name: Baxter_biosketch_earlyindependence.pdf

Attach Current & Pending Support: File Name:

Tracking Number: GRANT12936134 Funding Opportunity Number: RFA-RM-19-008 . Received Date: 2019-09-13T15:56:35.000-04:00

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

NAME: Sally L. Baxter, M.D., M.Sc.

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Fellow

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Duke University (Durham, NC)	B.S.	05/2009	Biology (Major), Physics (Minor), Genome Science & Policy (Certificate)
London School of Hygiene and Tropical Medicine (London, United Kingdom)	M.Sc.	08/2010	Public Health
Perelman School of Medicine at the University of Pennsylvania (Philadelphia, PA)	M.D.	05/2014	Medicine
University of California San Diego (UCSD) Dept of Internal Medicine (San Diego, CA)	Internship	06/2015	Internal Medicine
UCSD Dept of Ophthalmology (San Diego, CA)	Residency	06/2018	Ophthalmology
UCSD Health Dept of Biomedical Informatics (San Diego, CA)	Fellowship	Present	Biomedical Informatics

A. Personal Statement

My goal for this proposed NIH Director's Early Independence Award is to become an independent investigator conducting translational research developing machine learning-based models to predict glaucoma progression that incorporate systemic attributes from electronic health records (EHRs) along with patient-generated data from novel smartwatch-based home blood pressure monitors and from flexible electronic medication adherence sensors. This will leverage my experience in ophthalmology, clinical epidemiology, biomedical informatics, data science, and artificial intelligence. I am one of the few ophthalmologists with formal training in informatics to develop and evaluate advances in information technology for clinical practice. Glaucoma remains a leading cause of blindness, and many patients progress despite seemingly adequate control of intraocular pressure. How systemic conditions influence glaucoma is not well understood. Investigating this relationship could improve understanding of glaucoma pathophysiology and identify novel therapeutic targets. Risk prediction models that integrate high-volume EHR data along with patient-generated data from wearable devices and sensors may facilitate clinical decision support tools to promote earlier diagnosis and/or treatment, which is critical given that vision loss from glaucoma is currently irreversible.

With my clinical training in ophthalmology, master's in public health, experience in clinical epidemiology, and my current biomedical informatics fellowship, I have a multidisciplinary background. I have a track record of seeing projects through to completion and a broad range of leadership experience, including leading a team that developed an award-winning informatics design proposal, overseeing a team studying EHR implementation on clinical workflows, serving as Chief Resident, and being captain of an 85-person NCAA Division I athletics team. Furthermore, I have already published work in the machine learning/artificial intelligence and biomedical informatics space. After my fellowship, I plan to build an independent research program integrating health information technology and data science to improve precision management of glaucoma. The NIH Director's Early Independence Award will be crucial for facilitating my transition to independence by providing essential resources and protected time to complete my aims.

1. **Baxter SL,** Marks C, Kuo TT, Ohno-Machado L, Weinreb RN. Machine learning-based predictive modeling of surgical intervention in glaucoma using systemic data from electronic health records. Am J Ophthalmol. 2019 Jul 16. doi: 10.1016/j.ajo.2019.07.005. [Epub ahead of print] PubMed PMID: 31323204.

2. **Baxter SL**, Gali HE, Huang AE, Millen M, El-Kareh R, Nudleman E, Robbins SL, Heichel CWD, Camp AS, Korn BS, Lee JE, Kikkawa DO, Longhurst CA, Chiang MF, Hribar MR, Ohno-Machado L. Time requirements of paper-based clinical workflows and after-hours documentation in a multi-specialty academic ophthalmology practice. Am J Ophthalmol. 2019 Mar 22. doi: 10.1016/j.ajo.2019.03.014. [Epub ahead of print] PubMed PMID: 30910517.
3. Kermany DS*, Goldbaum M*, Cai W*, Valentim CCS*, Liang H*, **Baxter SL* (Co-First Author)**, *et al.* Identifying Medical Diagnoses and Treatable Diseases by Image-Based Deep Learning. Cell. 2018 Feb 22;172(5):1122-1131.e9. PubMed PMID: 29474911. (*contributed equally)
4. Liang H*, Tsui BY*, Ni H*, Valentim CCS*, **Baxter SL* (Co-First Author)**, Liu G, *et al.* Evaluation and accurate diagnoses of pediatric diseases using artificial intelligence. Nat Med. 2019 Feb 11. doi: 10.1038/s41591-018-0335-9. PubMed PMID: 30742121.

B. Positions and Honors

Selected Positions and Employment

2004	Summer Research Intern, Gage Laboratory, Salk Institute for Biological Studies, San Diego, CA
2005-2009	Research Assistant, Sherwood Laboratory, Duke University, Durham, NC
2006	Summer Research Intern, Gage Laboratory, Salk Institute for Biological Studies, San Diego, CA
2007	Amgen Scholar, Kaufer Laboratory, University of California Berkeley, Berkeley, CA
2008	DukeEngage Intern, UCSD Center for Community Ophthalmology, San Diego, CA
2011-2013	Research Fellow, Penn Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA
2014-2015	Resident Physician, UCSD Department of Internal Medicine, San Diego, CA
2015-2018	Resident Physician, UCSD Department of Ophthalmology, San Diego, CA
2018-2019	Chief Resident, UCSD Department of Ophthalmology, San Diego, CA
2018-present	Staff Physician, Veterans Affairs (VA) San Diego Healthcare System Eye Clinic, San Diego, CA
2018-present	Fellow, UCSD Department of Biomedical Informatics, San Diego, CA
2018-present	Health Sciences Clinical Instructor, UCSD Department of Family Medicine and Public Health, San Diego, CA

Selected Honors and Awards

2005	Kyoto Prize Scholarship in Basic Sciences ($10,000 scholarship for academics and service)
2005	National Merit Scholarship ($2500 scholarship for academic talent)
2005-2009	Robert C. Byrd Honors Scholarship ($10,000 scholarship for academic performance)
2005-2009	Angier B. Duke Memorial Scholarship (4-year full merit scholarship at Duke University)
2007	Duke Presidential Research Fellowship ($2500 research funding for a scholarly project)
2007	Annual Biomedical Research Conference for Minority Students Outstanding Oral Presentation Award (Top Neuroscience presentation out of 116 abstracts)
2007	Duke Women's Track & Field All-Time #4 in Indoor Pole Vault, #5 in Outdoor Pole Vault
2008	All-Atlantic Coast Conference Academic Team
2008-2009	Team Captain, Duke University NCAA Division I Women's Track and Field
2008	United States Rhodes Scholarship Finalist
2009	*Summa Cum Laude* Graduation Honors, Duke University (Top 5% of graduating class)
2009-2010	United States Marshall Scholarship (Fully funded postgraduate scholarship in the UK)
2010-2014	Gamble Scholarship/21st Century Scholarship (4-year full tuition merit scholarship at Penn Med)
2013	Penn Clinical Epidemiology Research Prize (Top clinical epidemiology paper at Penn Med)
2014	Charles A. Oliver Memorial Prize for Highest Record of Performance in Ophthalmology
2017	California Academy of Eye Physicians and Surgeons Starr E. Shulman Fellowship
2017	Heed Ophthalmic Foundation Resident Retreat
2017	NEI Travel Grant for the Association for Research in Vision and Ophthalmology Annual Meeting
2017, 2018	UCSD Lamont Ericson, MD Award for Outstanding Patient Care by a Resident
2018-2019	Heed Ophthalmic Foundation Fellowship
2018	American Medical Informatics Association Student Design Challenge – 3rd Place Nationwide
2018-2020	National Library of Medicine Training Grant Postdoctoral Fellowship in Biomedical Informatics
2019	UCSD Public Health Research Day Poster Award – 3rd Place among Postdocs, Fellows, Faculty
2019	Selection to the *Journal of the American Informatics Association* Student Editorial Board (1 of 6 trainees nationwide)

Certification and Licensures

2014 California State Medical License – Active
2018 American Board of Ophthalmology – Board-eligible

C. Contributions to Science

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/sally.baxter.1/bibliography/public/

1. Investigating novel uses of electronic health records and patient-generated data for biomedical applications. The digitization of medicine, particularly through widespread adoption of electronic health records (EHRs), has resulted in exponential growth in electronic data. Advances in mobile and sensor technology and subsequent proliferation of wearable devices also offer additional sources of high-dimensional health-related data. I have been working on developing predictive models of glaucoma progression that leverage these novel data sources. I have developed predictive models incorporating EHR data on systemic conditions and medications (citation in Personal Statement section). I also supervised a team of medical students and ophthalmology residents in the formulation of a design proposal for using mobile patient-generated data in macular degeneration management, which received 3rd place nationwide in the American Medical Informatics Association Student Design Challenge. I am also actively investigating how these data are incorporated into existing clinical workflows to enable real-world translation of clinical predictions and other data-driven insights. To provide a baseline for comparison, I examined paper-based workflows in ophthalmology in detail and am currently conducting a study examining how EHR implementation affects ophthalmology workflows. To discuss the broader challenges of implementing artificial intelligence technologies that leverage some of these novel data sources, I wrote a narrative review that was published in *Nature Medicine* and am now endeavoring upon a systematic review focused on implementation of EHR-based predictive models in clinical practice.

1. He J*, **Baxter SL* (Co-First Author)**, Xu J, Zhang K. The practical implementation of artificial intelligence technologies in medicine. Nature Medicine. 2019 Jan ;25(1):30-36. PubMed PMID: 30617336. (*contributed equally)
2. Gali HE, Kuo DE, Yeh K, **Baxter SL**. Using mobile patient-generated data to monitor age-related macular degeneration in elderly individuals. American Medical Informatics Association Annual Symposium; 2018 November 06; San Francisco, CA, USA.
3. **Baxter SL**, Gali HE, Huang AE, Millen M, El-Kareh R, Nudleman E, Robbins SL, Heichel CWD, Camp AS, Korn BS, Lee JE, Kikkawa DO, Longhurst CA, Chiang MF, Hribar MR, Ohno-Machado L. Time-motion analysis of paper-based clinical workflows in a multi-specialty academic ophthalmology practice. Annual Meeting of the Association for Research in Vision and Ophthalmology; 2019 May 1; Vancouver, BC, Canada.
4. **Baxter SL,** Marks C, Kuo TT, Ohno-Machado L, Weinreb RN. Predictive Modeling of Glaucoma Progression using Electronic Health Records. National Library of Medicine Informatics Training Conference; 2019 June 24; Indianapolis, IN, USA.

2. **Developed novel approaches for analyzing different retinal imaging modalities**: I have completed studies related to novel approaches to analyzing retinal images. The first was centered on quantifying non-perfusion in ultrawide field fluorescein angiograms (UWFAs). We used UWFAs and a prototype measurement software to quantify areas of non-perfusion in patients with treatment-naïve proliferative diabetic retinopathy. We found that areas of non-perfusion occupying greater than a threshold size of 23% of the total retinal image were more likely to have associated NV that was more numerous and more posteriorly located. This demonstrated that UWFA can precisely quantify non-perfusion in PDR and can help identify patients needing closer follow-up or earlier intervention to avoid vision-threatening complications. I designed the study, collected patient images, hand-segmented the images, performed the analysis, collated the results, and wrote and edited the manuscript which has been published in *OSLI Retina*. The second study involved generating a diagnostic tool based on a deep learning framework to diagnose retinal optical coherence tomography (OCT) images. Our team analyzed over 200,000 OCT images to train a neural network that utilized transfer learning and achieved accuracy comparable to human physicians. This work was featured as a cover article of *Cell* (citation listed earlier in the Personal Statement). I trained our research team in retinal pathology and image

analysis and helped oversee the annotation of the images used to train the neural network. I helped analyze and interpret the data, contributed to drafting and editing the manuscript, and helped design a video abstract of our work for *Cell's* website.

1. **Baxter SL**, Ashir A, Nguyen BJ, Nudleman E. Quantification of Retinal Non-perfusion Associated With Posterior Segment Neovascularization in Diabetic Retinopathy Using Ultra-Widefield Fluorescein Angiography. Ophthalmic Surg Lasers Imaging Retina. 2019 Feb 1;50(2):86-92. doi: 10.3928/23258160-20190129-04. PubMed PMID: 30768215.
2. **Baxter SL**, Ashir A, Nguyen BJ, Nudleman E. Quantification of retinal nonperfusion associated with neovascularization in diabetic retinopathy using ultrawide field fluorescein angiography. In:Hood DC, editor. The Association for Research in Vision and Ophthalmology Annual Meeting; 2017 May 07; Baltimore, MD, USA. Invest. Ophthalmol. Vis. Sci. 2017; 58(8):93.
3. "Looking Deep: Rise of the Machines / Cell, February 22, 2018 (Vol. 172, Issue 5)." Cell Press Video Abstracts. https://www.youtube.com/watch?v=vg1OQExo4HM&sns=fb&fbclid=IwAR0j0C1LNSjRlOE2bIpMOlBNNUxGDI5ymy4_mccMOKufAjAt9db3DiIrAGc

3. **Employed a nationwide blindness registry in Belize to describe the epidemiology of blindness and inform public health planning for eye care services in a low-resource setting**: Avoidable blindness is a major public health problem, particularly in low-resource nations that carry a disproportionate burden of visual impairment globally. Knowledge of the epidemiology of blindness in these countries is often lacking, particularly since standardized population-based surveys may not have been conducted. Existing data from disease registries may serve as a surrogate and help inform healthcare service prioritization. By analyzing a nationwide blindness registry from the Belize Council for the Visually Impaired (BCVI), I found that cataract was the leading cause for blindness registration, followed by glaucoma and diabetic retinopathy. Examination of local data at the district level directly informed recommendations to the organization to optimize their services. Furthermore, I recommended measures to enhance the consistency and completeness of the data captured in their register. At follow-up four years later, many of my recommended interventions had been successfully implemented, such as strategies for increasing the cataract surgical rate and developing glaucoma and diabetic retinopathy screening programs, which lowered the rates of blindness registration for these treatable conditions. This study demonstrated that although registry data may not be ideal for calculating population-level measures such as prevalence, the patterns of disease captured by the register still represents valuable data for public health planning. For this work, I obtained the registry data from BCVI, conducted field work in Belize, analyzed the data, and with input from my MPH research advisors [redacted], formulated the recommendations which the organization then implemented. I subsequently wrote the manuscript and presented the work at multiple international forums.

1. **Baxter SL**, Wormald RP, Musa JM, Patel D. Blindness Registers as Epidemiological Tools for Public Health Planning: A Case Study in Belize. Epidemiology Research International. 2014 December 03; 2014:e659717.
2. **Baxter SL**. Commentary: Using Blindness Registers for Public Health Ophthalmology in Low Resource Settings. Journal of Clinical and Experimental Ophthalmology. 2016 May 18; 7(3):1000551.
3. **Baxter SL**, Wormald RP, Musa JM, Patel D. Leading causes of registration for blindness and low vision in Belize. The 22nd Congress of the International Society for Geographical and Epidemiological Ophthalmology; 2012 September 21; Hyderabad, India.
4. **Baxter SL**, Wormald RP, Musa JM, Patel D. Leading causes of registration for blindness and low vision in Belize. The 9th General Assembly of the International Agency for the Prevention of Blindness; 2012 September 18; Hyderabad, India.

4. **Clinical research studies in ophthalmology**: I have conducted several clinical research studies spanning a spectrum of areas in ophthalmology. First, as a medical student I performed a secondary analysis of data from the Systemic Immunosuppressive Therapy for Eye Disease Cohort Study to improve risk stratification of uveitic patients for choroidal neovascularization (CNV), an uncommon but sight-threatening complication of uveitis. Because CNV is treatable in the anti-VEGF era, identifying high-risk patients can facilitate early detection and reduce vision loss in this young working-age patient population. This study was awarded as the

single top Clinical Epidemiology paper at the University of Pennsylvania School of Medicine in 2013. During medical school I also wrote two textbook chapters in oculoplastics, with one focused on surgical management of facial palsy and the other focused on psychological disturbances in patients with thyroid eye disease. Finally, during residency I also wrote a case series to characterize clinical features among patients with restrictive strabismus resulting from prior pterygium excision and describe a surgical approach for successful treatment and resolution of their double vision.

1. **Baxter SL**, Pistilli M, Pujari SS, Liesegang TL, Suhler EB, Thorne JE, Foster CS, Jabs DA, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, Kempen JH. Risk of choroidal neovascularization among the uveitides. Am J Ophthalmol. 2013 Sep;156(3):468-477.e2. PubMed PMID: 23795984; PubMed Central PMCID: PMC3748230.
2. **Baxter SL,** Scawn RL, Korn BS, Kikkawa DO. Management of Facial Palsy. In: Expert Techniques in Ophthalmic Surgery. 1st ed. Ichhpujani P, Spaeth GL, Yanoff M, editors. New Delhi, India: Jaypee Brothers Medical Publishers; 2015. Chapter 55; p.481-490. 951p.
3. **Baxter SL**, Scawn RL, Korn BS, Kikkawa DO. Psychological Disturbances in Thyroid Eye Disease . In: Thyroid Eye Disease. Douglas RS, McCoy AN, Gupta S, editors. New York: Springer; 2015. Chapter 13; p.143-152. 157p.
4. **Baxter SL**, Nguyen BJ, Kinori M, Kikkawa DO, Robbins SL, Granet DB. Identification and correction of restrictive strabismus following pterygium excision surgery. Am J Ophthalmol. 2019 Feb 13. pii: S0002-9394(19)30055-8. doi: 10.1016/j.ajo.2019.02.004. [Epub ahead of print] PubMed PMID: 30771334.

5. **Used *Drosophila* models to explore novel therapies for hereditary spastic paraplegia**: Hereditary spastic paraplegia is a progressive neurodegenerative disease that can cause disabling spasticity and weakness. It can be modeled with *Drosophila* carrying mutations in the *spastin* gene. Under the mentorship of Dr. Nina Sherwood, I investigated whether cold treatment could improve behavioral and cellular phenotypes associated with *spastin* mutations. Cold temperature improved mobility and survival for *spastin* mutant flies and was also associated with partial rescue of defects in synaptic morphology due to *spastin* mutation. Not only did this support the potential use of hypothermia as a novel therapeutic approach for AD-HSP, it also highlighted the finding that neuronal phenotypes are potentially very sensitive to variations in temperature, which should be accounted for in studies of neurodegenerative phenotypes in model systems. I performed all elements of this project: basic fly husbandry; making appropriate genetic crosses to produce various mutant strains; measuring eclosion rate, climb rate, and lifespan for control and mutant flies maintained at different temperature settings at various stages in development; dissecting and immunostaining larval neuromuscular junctions to evaluate synapse morphology under different temperature treatment conditions; collating results and conducting the statistical analysis of the results; and writing the research manuscript. I also drafted half of a textbook chapter describing *Drosophila* models of AD-HSP and edited it in its entirety.

1. **Baxter SL**, Allard DE, Crowl C, Sherwood NT. Cold temperature improves mobility and survival in Drosophila models of autosomal-dominant hereditary spastic paraplegia (AD-HSP). Dis Model Mech. 2014 Aug;7(8):1005-12. PubMed PMID: 24906373; PubMed Central PMCID: PMC4107329.
2. Ozdowski EF, **Baxter SL**, Sherwood NT. Movement Disorders. 2nd ed. LeDoux MS, editor. Elsevier Inc.: Elsevier; 2014. Chapter 73, Drosophila models of hereditary spastic paraplegia 1103-1122p.

D. Research Support

Heed Ophthalmic Foundation Fellowship
Role: Principal Investigator
Dates: 7/1/18-7/1/19
Research support for projects during my biomedical informatics fellowship.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 03/31/2020

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ● No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

○ Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

❑ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

5. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

TRAVEL

[redacted] is requested per year for travel to professional conferences to present research findings, forge collaborations, and keep abreast of developments in both ophthalmology and informatics. Examples of conferences to be attended include the American Academy of Ophthalmology Annual Meeting, the Association for Research in Vision and Ophthalmology Annual Meeting, and the American Medical Informatics Association Annual Symposium.

COMPUTERS

As detailed in Facilities and Resources, in general Dr. Baxter will have computational resources provided by the institution. However, additional funding is requested for iPads for direct use in the research studies. iPads will be used to administer surveys for participating patients for Aims 2 (surveys regarding experience using blood pressure monitors) and 3 (surveys regarding experience using medication adherence sensors). Funds are requested to fund three iPads [redacted] each) so that multiple patients may complete the survey simultaneously. In addition, the iPads will be used for wireless data transfer of adherence data from the sensors. These will be purchased in year 1.

PARTICIPANT INCENTIVE PAYMENTS

Incentive payments for participants. All participants will be provided [redacted] for participating in research visits at initial enrollment when receiving the blood pressure monitors or medication adherence sensors. This proposed payment is required by our IRB to equate payments with other ongoing studies at the Shiley Eye Institute. The study will enroll ~200 patients (150 patients for Aim 2 + 20 patients for Aim 3 = 170 patients, plus additional 30 to account for dropout/loss to follow-up and/or possible need for iterative design workshops). Total incentive payment budget would be [redacted] * 200 = [redacted]. This will be divided between Years 2-4.

[redacted]

TRAINING

Micromasters in Data Science. This MicroMasters Program offered by UCSD encompasses 4 courses – (1) Python for Data Science ([redacted]), (2) Probability and Statistics in Data Science using Python ([redacted]), (3) Machine Learning Fundamentals ([redacted]), and (4) Big Data Analytics Using Spark ([redacted]). The curriculum would be completed over Year 1.

[redacted]

Clinical Research Enhancement through Supplemental Training (CREST) Courses. Dr. Baxter will enroll in CREST courses to obtain specific targeted training in clinical research areas such as data management and informatics, advanced statistics electives, and research budgeting and project management. Current costs for faculty enrollment is [redacted] per 2-unit course. Dr. Baxter will complete 2 courses each in Years 2 and 3.

[redacted]

Clinical Informatics Board Review Course. AMIA offers a Clinical Informatics Board Review Course (CIBRC) Bundle that Dr. Baxter will complete to prepare for successful subspecialty board certification in Clinical Informatics. This will be in Year 2.

[redacted]

Assorted Training Activities/Workshops. The Qualcomm Institute offers a highly rated Seminar Series that will complement Dr. Baxter's training and expand her knowledge of different aspects of predictive analytics and data science. These include the Big Data Day Camp series and the Amazon Web Services series. Academic registration for faculty for these events costs ~[redacted]. Dr. Baxter plans to attend ~2 on average per year during the award period.

[redacted]

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	
Research Plan Section	
2. Specific Aims	specificaims_final.pdf
3. Research Strategy*	researchstrategy_final.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	
9. Letters of Support	merged_lettersofsupport_v2.pdf
10. Resource Sharing Plan(s)	
11. Authentication of Key Biological and/or Chemical Resources	
Appendix	
12. Appendix	

Tracking Number: GRANT12936134
Funding Opportunity Number: RFA-RM-19-008. Received Date: 2019-09-13T15:56:35.000-04:00

SPECIFIC AIMS

Research Objectives: Glaucoma is the leading cause of irreversible blindness globally and will affect >110 million people by 2040. It entails progressive optic nerve degeneration which leads to visual field loss. A precision medicine approach to facilitate early detection and treatment is critical, given that symptoms typically do not present until the disease is advanced. This is particularly important for racial minorities such as African Americans and Latinos, who exhibit earlier onset of glaucoma, more rapid progression of disease, and are historically underrepresented in clinical research. **My long-term objective is to develop a multi-modal health information technology framework to improve risk stratification and generate novel therapeutic approaches for a diverse body of glaucoma patients.** In this application, I will address areas of glaucoma management underserved by current clinical practice: (1) understanding how systemic vascular conditions, such as hypertension, and their management impact glaucoma, and (2) developing innovative methods of measuring and promoting glaucoma medication adherence. I will complete the following aims to lay the foundation for informatics-enabled interventions that will ultimately contribute to reducing glaucoma blindness.

1. **Develop machine learning-based predictive models classifying patients at risk for glaucoma progression using systemic EHR data from a diverse nationwide patient cohort**. In preliminary studies, I found that systemic data from the EHR of a single institution demonstrated predictive value in forecasting glaucoma progression. I will expand upon this work by developing models using data from the *All of Us* Research Program, a nationwide, NIH-sponsored longitudinal patient cohort with >230,000 total participants to date and a focus on diverse representation. Using big data and state-of-the-art data science techniques in predictive analytics, I will develop robust and generalizable predictive models based on EHR data and other available data types that will better elucidate the role of systemic conditions in glaucoma.
2. **Evaluate how integrating blood pressure (BP) data from novel smartwatch-based home BP monitors enhance predictive models for risk stratification in glaucoma**. My preliminary studies demonstrated that BP data is important for predicting glaucoma progression. Novel smartwatch-based home BP monitors may offer more granular BP data, including nighttime measurements, that can better risk stratify glaucoma patients. I will obtain glaucoma patients' data regarding circadian regulation of BP, sleep, and physical activity at home using novel smartwatch devices and evaluate for associations with markers of glaucoma progression, leveraging deeply phenotyped clinical research cohorts at UCSD.
3. **Measure glaucoma medication adherence using innovative flexible electronic sensors to validate their use for future interventions aimed at improving adherence and clinical outcomes in glaucoma.** I am involved in pilot studies which have demonstrated that novel flexible undetectable electronic patch sensors placed on eyedrop bottles can accurately register glaucoma medication delivery. This offers a more precise measure of adherence compared with patients' self-report. I will deploy these sensors among a diverse group of glaucoma patients to evaluate its accuracy in real-world use. This will lay a foundation for developing future strategies to improve adherence and patient engagement in chronic disease management.

Institutional Support: My current department chairs and mentors, [redacted], will jointly appoint me as an Assistant Professor after my fellowship. They will ensure 80% protected time for research; other responsibilities will be limited. I will have dedicated workspace at the UCSD Shiley Eye Institute. Both departments will provide additional personnel and resources as needed. I will be integrated into the faculty community of both departments. This institutional support and protected time will help me achieve my research objectives and transition to independence.

Early Independence Rationale: As an ophthalmologist with dedicated training in public health and biomedical informatics, I am uniquely qualified to conduct cutting-edge multidisciplinary investigations. My leadership experiences, such as being Team Captain for Duke's NCAA Division I Track and Field program and UCSD's Chief Resident in Ophthalmology, will inform my abilities to lead a research team. The NIH Early Independence Award would provide resources to rapidly build an independent research program and become a leader in data science, machine learning, and health information technology innovations to improve patient care and vision outcomes. These innovations in health information technology (EHRs, sensors, wearables, data integration) could also be applied to other diseases besides glaucoma, broadening the potential impact of my work.

RESEARCH STRATEGY

1. Rationale for abbreviating the typical post-doc phase: After completing my ophthalmology residency in June 2018, I have pursued dedicated research training in biomedical informatics through a postdoctoral fellowship funded by the National Library of Medicine (NLM). I have had >75% protected time for research, which has allowed me to develop and lead projects while under the supervision of outstanding mentors in both ophthalmology and informatics. This fellowship has provided a superb foundation to launch my independent line of inquiry at this intersection between multiple fields. I am seeking independence rather than pursuing additional post-doctoral training to maximize my potential impact at an earlier stage.

2. Evidence of transition to an independent position: I do not currently have research independence. I received my MD degree in 2014 and finished my ophthalmology residency on June 30, 2018, which falls within the eligibility window for this award. I had not served as postdoctoral fellow in any capacity following a previous doctoral degree. My current research agenda is set through concurrence with mentors, including [redacted] (UCSD Health Department of Biomedical Informatics [DBMI]) and [redacted] (UCSD Department of Ophthalmology). I am funded by an NLM T15 institutional training grant, of which [redacted] serves as PI. I do not have any space assigned directly by the institution for the conduct of my research. I require special waiver or exemption from UCSD to apply for NIH R01 grants. There are no arrangements to assume an independent research position that would begin prior to this award.

3. Personal/career development plan: My long-term objective is to become an independent physician-scientist working at the interface of ophthalmology and biomedical informatics, developing innovations in health information technology (IT) to better understand, prevent, and treat vision-threatening diseases. To improve outcomes, research innovations in health IT need to be translated for real-world clinical applications. My perspectives as a clinician and an informatician are critical for this translation.

Training and Research Experience (Strengths): My research interests have long been focused on a population-based approach to health and disease. I was one of a select few American students awarded the Marshall Scholarship, which funded my Master of Science in Public Health at the London School of Hygiene & Tropical Medicine. During the program I received foundational training in biostatistics, epidemiology, and public health principles (see Table 1). My master's thesis, which centered on patterns of blindness registration in Belize and how that information was used to inform public health planning of eye care services, allowed me to gain experience working with a large dataset, further develop my understanding of epidemiology beyond the classroom, and gave me insights into the context of data in the workflows of an organization. My experiences in clinical research continued to deepen throughout medical school and residency. I conducted a clinical epidemiology project to characterize risk factors for choroidal neovascularization in uveitis patients, which I published as first author in the *American Journal of Ophthalmology (AJO),* presented at the 8th International Symposium on Uveitis, and received the Penn Med Clinical Epidemiology Research Prize. In residency, I conducted research across a wide range of areas and subspecialties within ophthalmology. I wrote textbook chapters describing surgical techniques for facial nerve palsy and the psychological disturbances seen in patients with thyroid eye disease, demonstrated that quantitative analysis of retinal images could produce a screening threshold for proliferative diabetic retinopathy (first-author paper in *OSLI Retina*), and wrote a case series characterizing patients with restrictive strabismus after pterygium excision (first-author paper in *AJO*).

When I started working on developing deep learning algorithms to generate diagnoses from retinal images (co-first author paper in *Cell*), I realized that data science and AI would be a new frontier in ophthalmology. After several more projects in this space (resulting in two co-first author papers in *Nature Medicine*), I knew that I had found my focus. The promise of "big data" is immense, but trained physician-scientists who can bridge the research advances with real-world clinical practice are needed to realize that promise. The desire to not only understand how health data can be modeled and mined for discovery, but also how data presentation and delivery in healthcare settings can be optimized for improving patient care, led me to seek fellowship training.

As a postdoctoral fellow in biomedical informatics, I am engaged in a range of foundational coursework (Table 1) and am leading a number of research projects. I have gained experience in a wide array of tools and techniques. Finally, I am building a network of informaticians across UCSD, Rady Children's Hospital, and the San Diego Veterans Affairs (VA) Healthcare System.

Table 1. Prior coursework related to the conduct of research. Research-related coursework completed while an undergraduate at Duke (D), master's student at the London School of Hygiene & Tropical Medicine (L), medical student at the University of Pennsylvania (P), and resident/fellow at University of California San Diego (U).

Topic Area	Course	Topic Area	Course
Epidemiology	Basic Epidemiology (L)	Research	Principles of Social Research (L)
	Epidemiology & Control of Communicable Dis (L)	Design	Health Services (L)
			Introduction to Health Economics (L)
Statistics	Probability and Statistical Inference (D)		Health Care Evaluation (L)
	Basic Statistics for Public Health and Policy (L)		Designing Clinical Research (U)
	Statistical Methods in Epidemiology (L)		Health Services Research (U)
	Advanced Statistical Methods in Epidemiology (L)		Current Trends in Biomedical Informatics (U)
	Statistics Concepts for Biomedical Research (U)		Principles of Biomedical Informatics (U)
			Informatics in Clinical Environments (U)
Ethics	Issues in Medical Ethics (D)		Modeling Clinical Data for Computation (U)
	Research Ethics (P)		Data Management and Informatics (U)
		Research	Writing in Biology (D)
		Writing	Grant Proposal Writing Practicum (U)

Apart from my multidisciplinary training background, I also have strengths in organization, leadership, and conflict resolution, which will be critical for leading a research team. Details are provided in section 4.

Need for Additional Training (Weaknesses): I have several areas of further training to pursue in order to achieve my research objectives and maximize my impact. Areas of **additional technical expertise (Training Goal 1)** that I will develop further include: increased familiarity of advanced statistical techniques for predictive analytics, particularly for management of massive datasets and increased fluency in programming languages. I will also gain a **deeper understanding of the architecture of the information systems underlying healthcare delivery (Training Goal 2)**. Understanding the operational environment will be critical for translating health IT innovations into clinical practice. I will also pursue Clinical Informatics subspecialty board certification during the award period. Finally, I will deepen my experience in **leadership, communication, and ethics (Training Goal 3)** to rapidly transition from trainee to faculty investigator. I will take courses, participate in mentorship programs, and complete development programs specifically for junior faculty in the Health Sciences, such as the National Center of Leadership in Academic Medicine (NCLAM) program.

The NIH Director's Early Independence Award would provide funding, resources, and protected time to establish my research program, build upon my strengths, and advance my skills in areas where I need further development, as outlined above. This protected time is essential as a clinician. With the protected time and funding, I will be able to complete educational activities necessary for my development (Table 2).

If I am not selected, I will pursue funding from other mechanisms, such as the NIH K series, private philanthropic foundations, or the VA. I am fully committed to an academic research-based career.

Table 2. Educational activities to complete training goals during the award period.

Training Goal	Mechanisms by which training goal will be accomplished	Timeline
Training Goal 1: **Technical Expertise**	San Diego Supercomputer Center MicroMaster's in Data Science: Python for Data Science, Probability & Statistics in Data Science using Python, Machine Learning Fundamentals, Big Data Analytics Using Spark	Y1
	CREST course, CLRE 255: Data Management and Informatics	Y2
	CREST course, CLRE 263: Longitudinal Data Analysis	Y2
	CSE 255: Data Mining and Predictive Analytics	Y3
	Qualcomm Institute Amazon Web Services Seminar Series	Y1-5
	Halıcıoğlu Data Science Institute Distinguished Lecturer Series	Y1-5
Training Goal 2: **Operational Environment**	UCSD Information Services Medical Directors Committee	Y1-5
	UCSD Clinical Decision Support Oversight Committee	Y1-5
	Board Review Course for Clinical Informatics Subspecialty Board Certification	Y2
Training Goal 3: **Leadership, Communication, and Ethics**	UCSD Biomedical Ethics Seminar Series	Y1-5
	NCLAM Program for Junior Faculty in the Health Sciences	Y1
	CREST Course, CLRE 258: Project Management	Y3
	"My First R01" Program for Junior Faculty	Y4

4. Evidence of training ability and leadership: I have engaged in a wide range of activities to develop leadership and management capabilities that will prepare me to become a leader of a research team and mentor to future trainees. **As a postdoctoral fellow, I have led and mentored trainees in several capacities.** Within the first month of my fellowship, I assembled a team of ophthalmology residents and medical students to develop a design proposal for home-based monitoring of macular degeneration, a submission which ultimately won 3rd place at the American Medical Informatics Association Student Design Challenge. Last fall, I studied the impact of various quality improvement measures during the implementation of an electronic health record (EHR) in ophthalmology. In addition to designing the study and obtaining buy-in from relevant stakeholders, I recruited and organized 12 undergraduates and medical students to help obtain time-motion data from the clinics of nine ophthalmology faculty across three study phases (before EHR implementation, six weeks after implementation, and six months after implementation). I conducted didactic training sessions as well as paired observations to ensure high-quality data acquisition and inter-observer consistency. I am also mentoring several undergraduates, medical students, and ophthalmology residents across a spectrum of clinical research projects. Several of my mentees have had presentations accepted at national and international meetings and publications in peer-reviewed journals.

I have also had leadership roles in several non-research settings. One of my most substantial leadership experiences came from serving as **Team Captain of the NCAA Division I Women's Track and Field Team at Duke University**. I led team practices and workouts, worked to support the morale of all team members, and mediated any conflicts that arose between teammates. As a student-athlete and a team leader during the Duke Lacrosse scandal and the years immediately following it, I received in-depth training on recognizing sexual harassment and building an environment geared toward inclusion and diversity. I also attended a structured leadership development curriculum for all team captains on topics such as communication techniques, conflict resolution, formulating a team mission, and executing long-term and short-term goals.

Another major leadership role was being appointed by unanimous vote of residents and faculty as sole **Chief Resident for my ophthalmology residency**. I served as the key point of contact for scheduling, academic curriculum, personal issues, and clinical coverage concerns for all UCSD ophthalmology residents. Through creating and monitoring all vacation schedules, rotation schedules, call schedules, Grand Rounds and lecture schedules, while simultaneously balancing competing concerns regarding resident wellness, faculty support, and clinic flow, I developed a high level of organization and communication skills that will help me as I manage competing demands from overseeing a range of personnel as a Principal Investigator.

To obtain more formal training in leadership and management, I have obtained **certified training in Project Management** through the UCSD Health Sciences Information Services division and the San Diego chapter of the Project Management Institute. I am also registered for the **Mini-MBA for Health Sciences Professionals** offered by the UCSD Rady School of Management, to be completed in Fall 2019.

5. Host institution interactions: I am fortunate to have had several years of experience at my host institution of UCSD as a trainee and thrilled to have an opportunity to establish a research program here as faculty. Currently as a postdoctoral fellow, I have mentoring relationships with [redacted]. I have also received statistical support from [redacted] They will continue to provide feedback and input when I become a junior faculty member, but I will begin establishing independence by setting my own research agenda, delving into investigations that lie outside their existing research programs, and seeking independent collaborations. They have already provided me with a high level of autonomy during my postdoctoral fellowship and have committed to supporting my path to independence.

To stay involved in the broader scientific community at UCSD, I will continue attending departmental Grand Rounds and seminars in my departments in addition to group meetings with my collaborators as they pertain to my projects. Both ophthalmology and informatics host visiting speakers, who deliver a formal lecture, which is followed by a reception, providing additional opportunity for networking. I will attend departmental retreats and social events, which are hosted both on campus and at conferences. The UCSD Health Services Information Services group hosts several large gatherings focused on specific informatics topics, such as the UC Telemedicine Summit, UC Health Data Day, and Population Health Boot Camp. I attended these events as a fellow and will continue to engage in these events to integrate into the informatics community. I will also interact with the broader UCSD community through NCLAM and other career development programs.

6. Research challenge:

The Public Health Relevance of Glaucoma and the Need for a Precision Medicine Approach: Glaucoma is the world's leading cause of irreversible blindness and is projected to affect >110 million people by 2040. It entails progressive degeneration of the optic nerve that can lead to visual loss and blindness.[3] Visual impairment due to glaucoma is associated with decreased quality of life, psychiatric disorders such as depression and anxiety, and increased costs to patients, caregivers, and the health system. Early detection and treatment are critical, because symptoms do not present until glaucoma is advanced.

The need for a precision medicine approach is crucial in glaucoma. Given the potentially devastating consequences of undiagnosed advanced glaucoma, not only on the eyes but across a spectrum of outcomes, it is critical to identify individuals who are at greatest risk of developing the disease and who are at greatest risk of progressing quickly to vision loss. With this knowledge, clinicians can appropriately tailor treatment approaches, determine follow-up intervals for ongoing monitoring, and more effectively engage patients. Of note, minority populations, such as African Americans and Latinos, carry a disproportionate glaucoma burden. They have higher risk of developing glaucoma at younger ages, more rapid disease progression, and greater risk of becoming blind compared with Caucasians.[14–21] However, they are less well-represented in clinical research studies, and understanding precision management for minorities remains a work in progress.

Gaps in Current Clinical Practice Regarding Precision Management of Glaucoma: Currently, much of the vision research community's work in precision management of glaucoma is focused on technological innovations in structural and functional testing of the eyes, such as high-resolution ocular imaging and standardized visual field testing with automated algorithms for glaucoma progression analysis. These have been important innovations, many of which have migrated into clinical practice and have been adopted as standard of care. However, precision management of glaucoma is incomplete without accounting for the patient's co-existing systemic conditions, concurrent systemic medications/treatment, and their adherence with prescribed glaucoma treatment. Their importance is outlined below:

(1) The role of systemic conditions and medications in glaucoma: Lowering intraocular pressure (IOP) is the current mainstay of glaucoma therapy. However, not all patients with glaucoma have high IOP, and many patients progress to significant visual impairment despite IOP lowering. There has been increasing interest in identifying other therapeutic targets besides IOP.

Vascular conditions such as hypertension, diabetes, and coronary artery disease have been hypothesized to have a role in glaucoma development and progression. The relationship between systemic hypertension and primary open-angle glaucoma (POAG) is of particular interest, as both are age-related chronic diseases that are increasing in prevalence. Several population-based cross-sectional studies, such as the Rotterdam Eye Study and the Egna-Neumarkt Glaucoma Study,[24] have demonstrated an association between elevated blood pressure (BP), elevated IOP, and glaucoma. The Blue Mountains Eye Study also demonstrated that systemic hypertension is related to an increased risk of glaucoma and found that this elevated risk was independent of the effect of elevated BP on raising IOP. However, the relationship between BP and glaucoma is multifaceted, as the Barbados Eye Studies showed that *lower* systolic BP was also associated with risk of developing glaucoma. Several subsequent studies found that hypotension is a risk factor for glaucoma, and specifically reduction of BP at night, known as nocturnal dipping, appears to make the optic nerve more susceptible to damage. However, many of these prior analyses did not account for co-existing vascular conditions, such as diabetes, which could also potentially influence the perfusion of the optic nerve. Moreover, the medical treatment of systemic hypertension, which may have a major confounding effect, was not routinely examined. Understanding how hypertension, one of the world's most common conditions, impacts glaucoma progression will therefore have growing public health significance. The current gap in detailed knowledge regarding how hypertension impacts glaucoma progression is a critical unmet need.

(2) Understanding glaucoma medication adherence: Initial lowering of IOP is most often achieved through daily use of eye drops. Unfortunately, compliance with eye drops has been reported to range from 30% to 80%. Moreover, patients' overestimate their own adherence compared to device-measured or pharmacy refill data. Some contributors to non-adherence include the lack of visual symptoms in the early and intermediate stages of the disease, lack of information or education regarding the disease process and the irreversibility of vision loss from glaucoma, need for lifelong treatment, and the cost of treatment. Medication non-adherence is a critical barrier to glaucoma management, as it can hasten disease progression and lead to eventual blindness. Currently, most glaucoma providers simply ask patients to self-report their adherence, which is notoriously unreliable. The lack of

reliable integration of adherence data into clinical workflows represents a lost opportunity for patient engagement and for improving clinical outcomes.

Health IT: An Innovative Approach to Precision Management of Glaucoma: I propose applying advancements in health IT to address these gaps, using state-of-the-art methods in data science (specifically big-data predictive modeling) coupled with integration of innovative data sources such as wearable devices for BP monitoring and medication adherence sensors. Health IT has rapidly advanced in the last decade, fueled by federal initiatives mandating electronic health record (EHR) adoption.[redacted] With wide EHR adoption,[redacted] vast quantities of clinical data are readily available that can be leveraged to better understand the relationship between systemic conditions and glaucoma. EHR data have been employed to develop prediction models in a wide range of clinical applications, such as predicting major post-surgical complications,[redacted] sepsis,[redacted] thirty-day readmission,[redacted] and death.[redacted] Outside the hospital, EHR-based prediction models have also been developed for outpatient conditions, such as predicting asthma exacerbations,[redacted] heart failure,[redacted] and substance abuse.[redacted] Computational advancements have facilitated the use of machine learning techniques to effectively perform classification tasks in medicine using EHR data.[redacted] In ophthalmology, several models have been developed to predict glaucoma onset and progression based on structural and functional data related to the eye,[redacted] although few have used systemic data from the EHR. However, the EHR is not the only source of "big data." Recognizing that encounters in clinical healthcare settings represent only a narrow snapshot of the patient experience, patient-generated data may help provide a more complete picture of human health. These patient-generated data may arise from mobile health applications, wearable devices, or other sensors designed to capture more detailed and representative information about each patient's experience.

Therefore, in addition to developing robust predictive models of glaucoma based on systemic EHR data from massive diverse patient cohorts, I will also expand upon EHR-based predictive models of glaucoma using patient-generated data derived from novel smartwatch home BP monitors (Omron HeartGuide Monitor; Omron Corporation, Kyoto, Japan), as well as investigational flexible electronic sensors that offer a more accurate representation of medication adherence. **I hypothesize that these data will offer predictive value in classifying patients at high risk of glaucoma progression and will therefore provide additional useful information for clinical decision-making (Fig. 1).** These findings will lay the necessary foundation for future health IT-related interventions, such as presenting relevant EHR and patient-generated data to both providers (via clinical decision support or dashboards in the EHR) and patients (via EHR patient portals or mobile health apps). This will advance the field by facilitating precision management of glaucoma.

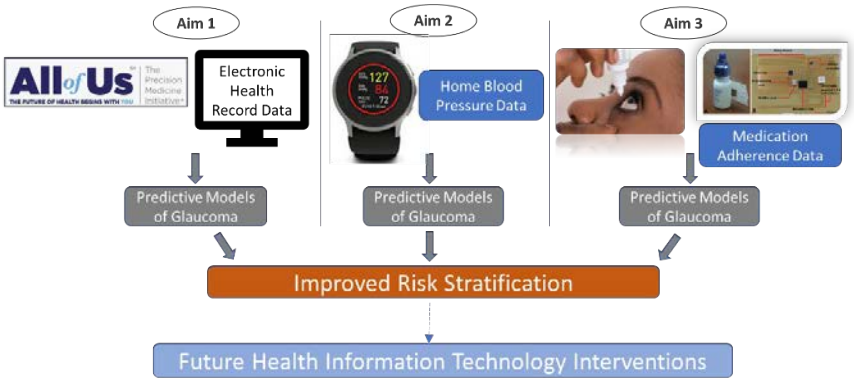

Figure 1. Multi-modal health information technology (IT) framework for enhancing precision management of glaucoma.

I chose this challenge to begin my independent research career because of my long-standing interest in public health. During my masters', I partnered with the Belize Council for the Visually Impaired and analyzed its national blindness registry to determine the epidemiology of eye diseases, identify gaps in coverage, and formulate recommendations for optimizing care delivery.[redacted] Early screening for glaucoma and diabetic retinopathy were priority recommendations across all districts. In my practice in the U.S., I have encountered numerous patients who have lost vision due to advanced pathology that was potentially preventable – clearly, avoidable blindness is a universal challenge and not limited to the developing world. My proposal focuses on glaucoma given its insidious nature and its prevalence. I am uniquely qualified to tackle this challenge as one of the few ophthalmologists with formal training in both public health and biomedical informatics.

7. <u>Approach:</u> I propose an innovative multi-modal health IT framework to improve risk stratification in glaucoma, with a focus on systemic conditions (particularly BP) and glaucoma medication adherence. **I will use state-of-the-art techniques in predictive modeling to investigate the predictive value of systemic data from the EHR (Aim 1), smartwatch-based home BP monitors (Aim 2), and flexible electronic sensors detecting glaucoma**

medication adherence (Aim 3). Understanding the predictive value of these various data types, which have not been previously investigated, will form the foundation for future health IT interventions to improve precision management of glaucoma.

Preliminary Data: My preliminary analyses centered on using systemic EHR data from a racially diverse patient cohort to train models of glaucoma progression, indicated by need for a glaucoma surgery within 6 months. Surgery was used as a surrogate for progressive disease because it was a clearly defined discrete event in the EHR.

Hypothesis: Data-driven modeling of systemic attributes from existing EHR data could predict glaucoma progression.

Methods: I included all adults (18 years and older) diagnosed with primary open-angle glaucoma (defined by International Classification of Disease [ICD] codes ICD-9 365.11 or ICD-10 of H40.11) between 9/1/2013 and 9/1/2018 with at least 6 months' of data in the UCSD EHR. This cohort consisted of 385 patients, 174 of whom had undergone glaucoma surgery within 6 months of presentation, and 211 who did not. Structured data were extracted from the UCSD Epic Clinical Data Warehouse pertaining to patient demographics, medications, information about admissions/hospitalizations, social history, vital signs, laboratory results, disease diagnoses, and procedures/surgeries.

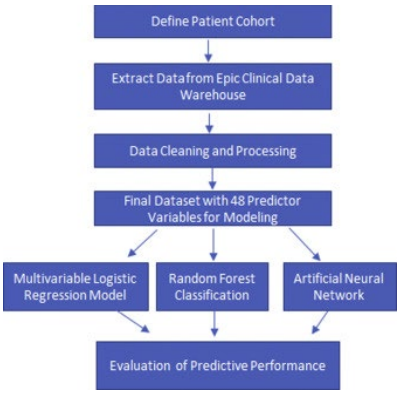

Figure 2. Workflow diagram for preliminary studies of prediction models of glaucoma progression

Data were transferred to a secure HIPAA-compliant server and exported to R[3] for processing and analysis (Fig. 2). The following libraries were used: *tidyverse, icd, varhandle, tableone, PerformanceAnalytics, ROCR, randomForest, neuralnet, cutpointr*, and *psych*. All codes for data cleaning, processing, and analysis are released on GitHub. After data cleaning, a total of 48 predictor variables (11 continuous, 37 categorical) were included for training the subsequent prediction models. Predictive models were constructed using multivariate logistic regression, random forests, and artificial neural networks (ANNs). For evaluation, we used a leave-one-out cross-validation approach, in which the model is trained on all observations except one, which then serves as the test set. We used five evaluation metrics of predictive performance: area under the receiver operating characteristic curve (AUC), sensitivity, specificity, accuracy, and the Youden Index.

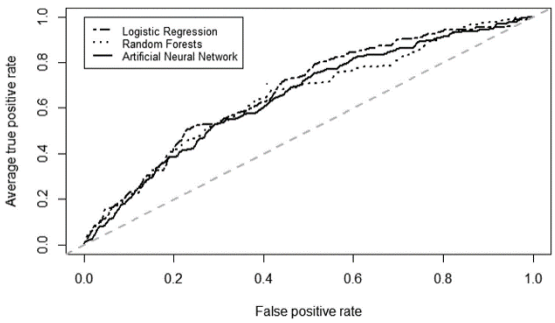

Figure 3. Average receiver operating characteristic curves for prediction models of glaucoma progression based on EHR data.

Results: Mean age in both groups (those who needed surgery and those who did not) was 73 years. Patients undergoing surgery were approximately equally split between males and females. Out of 385 patients, 80 (20.8%) of patients self-identified as African American or Hispanic. An additional 72 (18.7%) self-identified as "Other Race," "Mixed Race," or "Multi-Racial."

Average receiver operating characteristic curves for the predictive models are depicted in Figure 3. Multivariable logistic regression performed the best, with a mean AUC of 0.67, followed closely by random forests and ANNs at 0.65 (Table 3). All three methods had comparable accuracy, ranging from 0.60 (ANNs) to 0.62 (logistic regression and random forests). The logistic regression model had the highest Youden Index at 0.26 (Table 3).

Table 3. Predictive performance metrics.

Predictive Model	AUC	Sens	Spec	Acc	Youden
Logistic Regression	0.67	0.75	0.50	0.62	0.26
Random Forests	0.65	0.55	0.68	0.62	0.24
Neural Networks	0.65	0.71	0.51	0.60	0.22

In the logistic regression model, protective factors against needing glaucoma surgery were greater number of days hospitalized, higher values for minimum recorded systolic BP, and being prescribed ophthalmic medication, non-opioid analgesics, anti-hyperlipidemic medication, macrolide antibiotics, and calcium blockers. Higher mean systolic BP increased risk of needing surgery. Similarly, BP-related metrics emerged as variables of importance in the random forests model based on the mean decrease in accuracy and mean decrease in impurity indices.

***Implications**:* The performance of these models supported the hypothesis that systemic data captured in the EHR has some predictive value on its own in classifying patients at risk of glaucoma progression, *even in the absence of eye-specific endpoints*. Additionally, BP-related metrics and certain medication classes carried significant weight in predicting glaucoma progression. **In this proposal, I will expand upon my preliminary studies by developing more robust predictive models based on a larger, multi-center dataset of diverse patients, incorporating BP measurements from novel home BP monitors, and validating medication adherence sensors that will reflect real-world medication use.**

Aim 1: Develop machine learning-based predictive models classifying patients at risk for POAG progression using systemic data from the EHR in large multi-center clinical databases.

***Background and Hypothesis**:* My preliminary studies showed that models based on systemic data from the EHR demonstrated predictive value in forecasting glaucoma progression among UCSD patients, demonstrating value in pursuing further investigation in this arena with larger datasets. To enhance the performance of the models, improve their generalizability, and ensure diverse patient representation, I will develop predictive models of glaucoma progression based on EHR data from the *All of Us* Research Program, a nationwide NIH-sponsored longitudinal patient cohort with a focus on diverse patient representation, with plans to enroll at least 1 million individuals. To date, over 230,000 individuals have already been enrolled. Although EHR data is known to have several limitations (such as missingness, variability of follow-up, and noise), the breadth, scope, and scale of EHR data have generated novel insights in many other clinical domains for further exploration with directed research studies such as prospective clinical trials. Because glaucoma remains an important public health challenge, leveraging systemic EHR data for better understanding the disease (or at least directing future research) is an important area of investigation. I hypothesize that models based on data from *All of Us* will demonstrate the predictive value of systemic data for glaucoma progression and exhibit improved performance compared to models developed at a single institution.

Preparatory Work: The *All of Us* Research Program will provide a Researcher Workbench for data access starting in Winter 2019. To gain access to the *All of Us* data, I will complete all required processes, including registration, research ethics training, and completion of a data use agreement. I will then create a workspace specific for this project and add collaborators. My primary collaborator for this project will be [redacted]

Data Extraction: I will use the *All of Us* Cohort Builder to create a cohort of glaucoma patients. Using the available data browser, the current number of participants with a diagnosis of glaucoma, open-angle glaucoma, or primary open angle glaucoma based on SNOMED concept coding is ~3200. As enrollment continues, I anticipate that these numbers will be even greater once the award period begins. For the cohort of glaucoma patients, I will extract all EHR data available in *All of Us* for model development. These will include sociodemographic data and data regarding diagnoses, medications, procedures, and laboratory assessments.

Application of Models and Evaluation of Performance: I will develop and train predictive models for glaucoma progression using the *All of Us* dataset and measure model performance based on the following metrics: AUC, sensitivity, specificity, accuracy, and Youden Index. Because my preliminary studies showed that logistic regression model was the overall best-performing model and additionally offers excellent interpretability, I will first focus on developing logistic regression models. To improve performance, I will also consider interaction terms and potential non-linear forms for some continuous predictors using the generalized linear models. Furthermore, I will improve reliability of model performance by removing redundant variables using the least absolute shrinkage and selection operator (LASSO) to perform variable selection. Unlike its classic counterparts, LASSO effectively addresses

multicollinear and high-dimensional variables. Then, I will develop and evaluate random forests models and neural networks with this dataset.

Power and Sample Size: Sample size calculations were performed in collaboration . We achieved an AUC = 0.67 in our pilot study for the predictive model developed based on the UCSD EHR with a sample consisting of 174 cases and 217 controls. Even with the single-institution study, we had 0.99 power to detect an AUC of 0.8 from the null of AUROC of 0.5 based on a two-sided alpha = 0.05. As the *All of Us* dataset far exceeds the UCSD dataset in size, we will have sufficient power for Aim 1.

***Expected Results*:** I expect that the predictive models of glaucoma progression trained with data from *All of Us* will demonstrate improved performance compared with the preliminary data from UCSD only. In particular, the neural networks will likely perform much better due to larger cohort size. I anticipate similar covariates will emerge as predictors of glaucoma progression, particularly those related to BP and medications.

***Potential Pitfalls and Alternative Approaches*:** The primary pitfall is if the go-live of the *All of Us* Researcher Workbench is delayed and not available during the award period. If the public access option is not available, I will work with to gain access, since she is one of the PIs of the *All of Us* Research Program and will be able to facilitate data access. Alternatively, I can use aggregated data from the five University of California (UC) academic medical centers as another large and diverse patient dataset option. Another consideration for this aim is high variability of data among patients in the cohort – different entry times and different follow-up lengths before observing the event of interest or censoring. To address this, I will develop longitudinal models with survival analyses. My training plan includes advanced courses in longitudinal statistical analyses, and I will also have the support of statisticians .

Aim 2: Evaluate how integrating BP data from novel smartwatch-based home BP monitors enhance predictive models for risk stratification in glaucoma.

Background and Hypothesis*:* BP-related variables emerged as important predictors of glaucoma progression in my preliminary studies. Prior studies have demonstrated nighttime blood pressure dysregulation in particular may confer elevated risk of glaucoma progression. In general, patients with abnormal circadian regulation of BP – in whom nighttime BPs may not decrease enough, decrease too much, or paradoxically rise – experience a significantly higher risk of a range of cardiovascular, neurovascular, and ocular complications. Traditional daytime clinic-based BP measurements, such as those recorded in the EHR, cannot identify these patients. The current standard for phenotyping circadian BP regulation is cuff-based ambulatory blood pressure monitoring, which is not used in routine clinical practice due to its cost and difficulty of use. I hypothesize that patient-generated data regarding circadian BP regulation derived from novel smartwatch home BP monitors will enhance prediction of glaucoma progression.

Study Population: I will recruit patients who are currently enrolled in the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES). , one of my mentors, serves as PI of these studies and will ensure my access to the data. They have already undergone extensive imaging and testing in relation to glaucoma status, such as visual acuity, intraocular pressure, ophthalmic examination, optic nerve photographs, optical coherence tomography (OCT) imaging of the optic nerve, optical coherence tomography angiography (OCTA) of the optic nerve and retina, and visual field testing to assess for functional damage from glaucoma. Drawing from existing study cohorts will lessen the burden of patient recruitment and maximize my ability to complete the project within the award period.
The DIGS cohort is a general study examining various diagnostic technologies in glaucoma, whereas ADAGES is specifically focused on patients of African descent, traditionally under-represented in clinical research studies.

UCSD is particularly well-suited to study these populations. Our ophthalmology clinics are incredibly high-volume, with >150,000 patient visits in 2018 at all UCSD locations. The Glaucoma clinics at UCSD have >20,000 annual patient visits, with high representation of African Americans (>3,000 annually) and Latino patients (>4,000 annually). This high representation of minority populations reflects the diversity of the surrounding region and UCSD's reputation as a leading glaucoma center. The UCSD Shiley Eye Institute has a proven track record of successful engagement and enrollment in clinical research studies, including minorities.

Eligibility Criteria: Participants will be recruited from the DIGS and ADAGES study cohorts at the UCSD Shiley Eye Institute and UCSD Hamilton Glaucoma Center. All participants must be 18 years old or older. Participants will be required to have at least one eye with open angles, best corrected visual acuity of 20/40 or better to be included. Participants taking a medication known to affect visual field sensitivity and eyes with a history of intraocular surgery (except uncomplicated glaucoma and cataract surgery), a secondary cause of elevated intraocular pressure, a coexisting intraocular disease affecting visual field, or a problem other than glaucoma affecting color vision may be excluded. Additional exclusion criteria include wrist circumference less than 5.3 in (13.5 cm) or greater than 8.5 in (25 cm), or cognitive or physical impairment that precludes the use of a wristwatch device. There are no eligibility criteria based on gender, race, or socioeconomic status.

Patient recruitment and enrollment: For eligible patients who provide informed consent to participate, an enrollment visit will be conducted at the UCSD Hamilton Glaucoma Center. Either prior to or at the enrollment visit, each participating patient will complete an online questionnaire using an electronic data capture form (UCSD REDCap) regarding their basic demographic information (i.e. age, sex, race), prior diagnosis of hypertension, use and timing of anti-hypertensive medications, prior hospitalization for very high or very low blood pressures, any prior diagnosis of abnormal nighttime blood pressures, any dietary modifications (e.g. low sodium diet), level of physical activity, general sleep patterns, baseline use of digital health technology, and perceptions of home health monitoring.

Home BP monitor use: At the enrollment visit, the patient will also be provided with a smartwatch home BP monitor. Research personnel will ensure appropriate fit/sizing and review how to use the monitor with the patient. The patient will then wear the smartwatch BP monitor for 1 week at home. The monitor will collect BP, pulse, activity data (i.e. number of steps, distance traveled, and calories burned) and sleep data (sleep patterns, sleep period of time, quality of sleep). The patient will be asked to wear the smartwatch home BP monitor at all times except for when showering or charging the device.

Data collection: At the follow-up study visit (1 week after enrollment visit), the patient will return the smartwatch home BP monitor to the UCSD Hamilton Glaucoma Center. All data recorded by the monitor (BP, pulse, activity, and sleep) will be imported into the study database. The total time commitment for each participating patient is about 1 week. As much as possible, study visits will be timed to coincide with the patients' existing study visits from DIGS or ADAGES at the UCSD Hamilton Glaucoma Center or with existing clinical appointments at the UCSD Shiley Eye Institute in order to minimize additional time and transportation burden. Each patient will receive a participation incentive payment of [redacted].

Data analysis: The data from the smartwatch home BP monitor will be processed to produce the following variables: average daytime systolic BP, average daytime diastolic BP, average nighttime systolic BP, and average nighttime diastolic BP. "Nighttime" will be defined as sleeping time, as monitored by the smartwatch.

The patient's circadian BP phenotype will be defined by the difference between average daytime systolic BP and average nighttime systolic BP using the following criteria: decrease of 10-20% from day to night will be defined as "normal dipper," greater than 20% will be defined as "extreme dipper," 0-10% will be defined as "non-dipper," and increase of BP from day to night will be defined as "reverse dipper." BP-related items from the questionnaire (i.e. previous diagnosis of hypertension, number of anti-hypertensive meds, any prior hospitalizations) will also be included as predictor variables. In addition to the BP variables, additional variables generated by the smartwatch home BP monitor will include pulse, activity, and sleep metrics such as average daytime pulse, average nighttime pulse, average steps per day, average distance traveled per day, average calories burned per day, and average hours of sleep per night.

Development of Models and Evaluation of Performance: Outcome variables will consist of markers of glaucoma progression, based on structural and functional testing of the eye already obtained in the DIGS and ADAGES studies. Predictive modeling will be performed using the same development and evaluation methods as outlined in Aim 1. In addition, I will measure predictive performance at baseline (EHR data only) and then again with inclusion of the data generated by the smartwatch home BP monitor, in order to evaluate how much improvement in predictive performance is gained by including the home BP monitor data.

***Expected Results*:** I hypothesize that the models that include the home BP monitor-generated data will perform better than models based on EHR data alone. This will be reflected by higher mean AUC, sensitivity, specificity,

accuracy, and Youden Index. In other words, the home BP monitor-generated data on circadian BP regulation will improve prediction of glaucoma progression.

***Potential Pitfalls and Alternative Approaches*:** Two study visits separated by 1 week may represent a disproportionate burden for patients, particularly those who are not local. This is not uncommon since the UCSD Shiley Eye Institute is a tertiary referral center and draws patients from a large geographical area. For patients who express difficulty returning for the follow-up visit, the option will be given to complete the follow-up questionnaire online and to return the smartwatch home BP monitor to the UCSD Hamilton Glaucoma Center via certified mail. In addition, all smartwatch home BP monitors will be tracked with radiofrequency identification (RFID) technology. This will minimize loss to follow-up and loss of equipment crucial to conducting the study.

Sample Size Justification: Based on the results from the preliminary analyses, I will have 80% power to detect an AUC of 0.65 from the null of AUC of 0.5 based on a two-sided alpha = 0.05 using data from 126 patients (63 patients with normal BP dipping profiles + 63 patients with abnormal dipping profiles). This is for measuring an outcome of glaucoma progression based on 0.5 decibel difference in visual field testing. Accounting for losses to follow-up and/or incomplete data in ~20% of patients, I will aim to enroll ~150 patients.

Future Directions: Should the smartwatch home BP monitor demonstrate predictive value, in the future I plan to develop a prototype workflow integrating the smartwatch home BP monitor data seamlessly with the UCSD EHR via Apple HealthKit. The rationale for this is that data from smartwatch home BP monitors are unlikely to be useful if clinicians are expected to manually review patients' raw BP data outside the EHR. Additionally, I would design a visualization tool to facilitate review of BP monitor data via a user-centered design process incorporating clinician feedback. I hypothesize that a direct data stream will facilitate physician engagement and enable real-world clinical application of circadian BP readings. Effectively translating risk prediction models into clinical practice will help reduce the burden of vision loss from glaucoma.

Aim 3: Measure glaucoma medication adherence using innovative flexible electronic sensors to validate its use for future interventions aimed at improving adherence and clinical outcomes in glaucoma.

Background and Hypothesis: Medication adherence is crucial for slowing progression of glaucoma. Because minority populations have been reported to have lower rates of medication adherence, this represents a key opportunity for intervention to improve outcomes and reduce disparities in this disease. Previous studies have been conducted with electronic monitoring devices for glaucoma,[redacted] but these devices were bulky and required additional effort from the patient for use. As such, they have not been adopted in clinical practice. My collaborators [redacted] have developed an innovative flexible electronic force sensor that can be embedded under the label of an eye drop bottle and therefore can be used by the patients *without any additional effort*. Thus, it is more likely to be effective in real-world use. This aim is geared toward preliminary data collection of adherence patterns among patients with glaucoma to validate the accuracy and usability of this novel sensor. I hypothesize that flexible electronic sensors will accurately detect glaucoma medication adherence among patients in real-world environments and reveal opportunities for future interventions to improve adherence.

Preliminary Studies: My collaborators [redacted] have pioneered the use of thin flexible electronics toward the development of a wireless electronic eyedrop system. Figure 4 displays the prototype flexible electronic sensor fitted beneath the label of an eyedrop medication bottle (A), example flexible electronics for both sensing and wireless transmission (B), and software developed for registering the timestamp of drop administration (C).

The flexible electronics system builds upon recently demonstrated multi-functional uses of ultra-thin, stretchable, flexible electronics for medical monitoring[redacted] that can be fabricated to be ultra-thin and imperceptible to the user. As shown in Figure 4, using [redacted] fabrication methods,[redacted] embedded beneath the adhesive label of the eyedrop bottle are ultra-thin flexible sensors,[redacted] stretchable antennas,[redacted] and integrated circuits for signal processing/wireless modulation. The prototype eyedrop system consists of a standard eyedrop bottle outfitted with flexible electronics for force/tilt sensing and Bluetooth low energy (BLE) transmission capabilities, as well as the

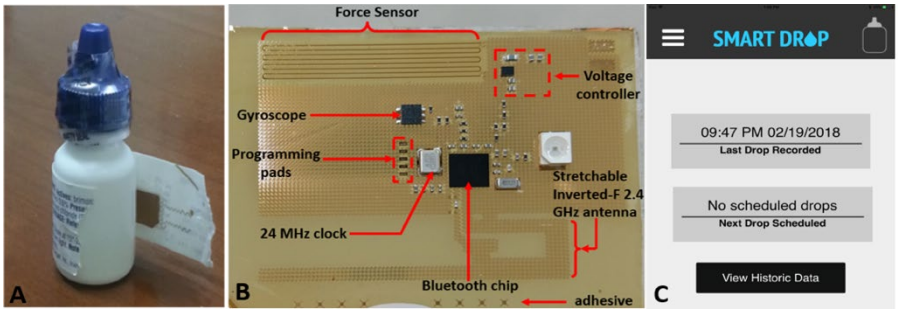

Figure 4. A: flexible electronic sensors embedded under the label of a bottle. B: Closeup of a flexible adhesive array of sensors, integrated circuits and antenna for sensing, processing and Bluetooth transmission. C: A smart phone application which can track eyedrop adherence from the instrumented bottle via Bluetooth and be programmed for reminders.

associated software on a mobile device. In the laboratory environment, 25 eyedrop bottles have already been fabricated and tested. They have demonstrated successful registration of force and tilt events associated with drop delivery. Preliminary data show successful functionality where each time the bottle is squeezed to deliver an eyedrop, a signal encoding the date and time is sent to a smartphone via Bluetooth; this information can then be archived or sent to a database for retrieval by a clinician or caregiver. Preliminary testing shows that the force sensor can sustain over 1,000 squeezes before the beginning of hysteresis of the force-sensitive sensor, wireless transmission over 150 feet, and continuous operation with miniaturized coin cell battery operation of over one month at 6 eyedrops delivered daily. This system reduces false positives for drop detection by registering administration of a drop only when the bottle is oriented to the correct angle and sufficient force is applied (thus obviating false positives when the bottle is bumped around in a purse or bag).

Eligibility Criteria: Eligibility criteria are the same as for Aim 2. Additional criteria specific to this aim include: currently self-administering eye medications and ownership and regular use of a smartphone device.

Recruitment, Inclusion and Data Collection: Patients will be recruited from DIGS and ADAGES. A [redacted] incentive payment will be given to patients who participate. Each consenting patient will be provided 2 eyedrop bottles with embedded sensors for each glaucoma medication they are currently prescribed. The bottles will be used consecutively, and since each eye drop bottle typically provides a 3-5 week supply of medication. In total, the 2 bottles will allow 6-10 weeks' worth of timestamped adherence data to be acquired for each prescribed medication. This length of time will allow detailed analyses of adherence patterns over a longitudinal period and capture day-to-day and week-to-week variations in adherence. The bottles will contain medications that the patient is already being prescribed as part of their standard clinical care.

A research coordinator will pair the bottle with a UCSD iPad so that wireless data transfer can ensue when the patient returns to Shiley for their follow-up visit. As is standard with glaucoma patients, patients are asked to bring their eyedrop bottles to their follow-up visit once they have completed the two bottles (approximately 6-10 weeks after initial enrollment). At the follow-up visit, the electronic sensor in the bottles will pair via Bluetooth with the UCSD iPad, which will then send the information securely to a HIPAA-compliant UCSD database.

Outcome Measurements: The primary goal of this exploratory aim is to validate the accuracy of this investigational sensor device for collecting adherence data in real-world settings. The external control metric or "gold standard" will be the difference in weight of the eye drop bottle between the initial enrollment (before medication administration) and at the follow-up visit (end of medication administration). The difference in weight will be used to determine the number of true doses that were administered by the patient. This will be compared with the number of doses recorded by the sensor. I will use ANOVA-based hypothesis testing to determine whether there was a statistically significant difference between the number of doses recorded by the sensor and the number estimated by weight difference in the bottles. Adverse events, such as difficulty experienced by the patient in administering medications due to the affixed sensor, detachment of the sensor from the bottle, and sensor breakdown or failure will be measured. These outcomes will help determine whether the sensor is feasible for deployment on a larger scale to obtain adherence data that can then be incorporated into predictive models or used to help guide patient engagement around medication adherence.

Potential Pitfalls and Alternative Approaches: The main pitfall is if the sensor does not function accurately under real-world conditions. I anticipate that the sensors will function accurately given the preliminary studies performed in laboratory settings. However, a key tenet of health IT development is to engage end-users, so these preliminary studies will enable glaucoma patients to trial the sensors and provide feedback. If major issues arise, then we will

plan human-centered design workshops to develop subsequent iterations of the prototype. These workshops will consist of 8-12 participants to provide feedback about their experience.

Sample Size: Initial validation of the sensors will be performed with 20 patients, which will reveal any major issues with adherence sensor use if they exist. Based on prior studies in human-centered design, this number is sufficient during the prototype development process.[100] Once the initial validation is complete, more wide-scale deployment to collect adherence data from a large number of patients can be conducted in the future.

8. Innovation: This study is highly innovative in several aspects: incorporation of systemic data from EHRs into predictive models of glaucoma, which currently focus on eye-specific structure and function metrics; leveraging state-of-the-art data science techniques in EHR data cleaning, processing, and modeling; integration of data from novel smartwatch home BP monitors, which only became commercially available in early 2019; and validation of an investigational wireless flexible electronic sensor for measuring medication adherence of eye drops, a form of adherence monitoring that has not been previously studied. These innovations in predictive modeling and investigating novel data types will form the foundation for future interventions aimed at timely and user-friendly delivery of health data to both providers and patients.

9. Relationship to previous work: Aim 1 will expand upon my prior work in developing EHR-based predictive models in glaucoma but broaden their scope and generalizability. Aims 2 and 3 will be new directions that are related to my prior work but distinct, due to their focus on patient-generated data and understanding integration between device/sensor data and EHR data for risk stratification. My previous mentors will remain my collaborators, which will be important to ensure I complete the aims as described. However, while I will seek their feedback and input, particularly at the beginning stages, I will conduct analyses and make plans for future studies independently. I will seek external input from new collaborators during the award period regarding my project, including faculty members in the UCSD Design Lab and the UCSD Institute for Public Health. I will secure independent grant funding for subsequent related studies as Principal Investigator.

10. Timeline: I will commit at least 9.6 person-months each year towards my Early Independence Award project in years 1-2, and equivalent effort to independent research in general in years 3-5. A timeline for career development and educational activities was provided in Table 2. Table 4 outlines the timeline for establishing my research team and achievement of scientific objectives.

Table 4. Timeline of research-related activities.

Activity	Y1	Y2	Y3	Y4	Y5
Securing workspace, purchasing computer workstations and general research supplies					
Hiring personnel					
Aim 1: Predictive Models using the *All of Us* Dataset					
• Register with All of Us, create workspace, build cohort					
• Data extraction, cleaning, and processing					
• Model development and evaluation					
• Compile results, prepare for publication and presentation					
Aim 2: Measuring Predictive Value of BP Monitors					
• Purchase monitors, finalize IRB approval and study protocol, train research assistants					
• Recruit patients, collect data					
• Analyze data, compile results, prepare for publication and presentation					
Aim 3: Validate Flexible Electronic Adherence Sensors					
• Purchase equipment for initial batch of sensors, finalize IRB approval and study protocol, train research assistants					
• Recruit patients, collect and analyze data					
• Prototype design iteration if needed					
• Compile results, prepare for publication and presentation					
Grant Preparation and Submission (NIH Grants, Institutional Grants, Foundation Grants)					

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

Are Human Subjects Involved	● Yes ○ No
Is the Project Exempt from Federal regulations?	○ Yes ● No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Multi-modal Health Information Technology Innovations for Precision Management of Glaucoma	No

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Multi-modal Health Information Technology Innovations for Precision Management of Glaucoma

1.2. Is this study exempt from Federal Regulations * ○ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	○ No
1.4.b. Are the participants prospectively assigned to an intervention?	● Yes	○ No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	○ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	○ Yes	● No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- Glaucoma

2.2. Eligibility Criteria

1. Aim 1 Eligibility Criteria: Adult (18 years and older) patients diagnosed with glaucoma (based on SNOMED concept coding, qualifying ICD diagnosis codes, treatment with glaucoma medications, or history of glaucoma-related procedure) included in the NIH-sponsored All of Us Research Program study cohort.

2. Aim 2 Eligibility Criteria: Participants will be recruited from the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES) cohorts at the UCSD Shiley Eye Institute and UCSD Hamilton Glaucoma Center. All participants must be 18 years old or older. Participants will be required to have at least one eye with open angles, best corrected visual acuity of 20/40 or better to be included. Participants taking a medication known to affect visual field sensitivity and eyes with a history of intraocular surgery (except uncomplicated glaucoma and cataract surgery), a secondary cause of elevated intraocular pressure, a coexisting intraocular disease affecting visual field, or a problem other than glaucoma affecting color vision may be excluded. Additional exclusion criteria include wrist circumference less than 5.3 in (13.5 cm) or greater than 8.5 in (25 cm), or cognitive or physical impairment that precludes the use of a wristwatch device. There are no eligibility criteria based on gender, race, or socioeconomic status.

3. Aim 3 Eligibility Criteria: Eligibility criteria are the same as for Aim 2. Additional criteria specific to this aim include: currently self-administering eye medications and ownership and regular use of a smartphone device.

2.3. Age Limits	Min Age:	18 Years	Max Age:	N/A (No limit)
2.4. Inclusion of Women, Minorities, and Children	WomenMinoritiesChildren.pdf			
2.5. Recruitment and Retention Plan	recruitment_retention.pdf			
2.6. Recruitment Status	Not yet recruiting			
2.7. Study Timeline	studytimeline.pdf			
2.8. Enrollment of First Subject	01/04/2021	Anticipated		

INCLUSION OF WOMEN, MINORITIES, AND CHILDREN

1. Inclusion of Women and Minorities

For all three aims of the study, there will be no exclusions on the basis of gender. Glaucoma has been reported to be more prevalent in women (61%) than men (39%),[redacted] so we will aim to achieve a gender breakdown of about 60%/40% female/male for each aim of the study. Aim 1 entails predictive modeling of glaucoma progression based on data from the *All of Us* Research Program national study cohort. Based on data available from the *All of Us* public data browser, women comprise 61.76% of the cohort, which is well-aligned with the distribution of glaucoma. Aims 2 and 3 involve active patient recruitment at UCSD, and we will actively recruit women for the study to meet a goal of 60% of enrolled patients.

Pregnant women will not be specifically excluded from the study. Their enrollment in will be unlikely overall since glaucoma tends to be an age-related condition that commonly presents once women have exited their childbearing years. Specifically, for Aim 3 (validation of flexible electronic sensors for measuring glaucoma medication adherence), enrollment of pregnant women will be highly unlikely as ophthalmologists typically discontinue use of intraocular pressure-lowering topical ophthalmic medications during pregnancy.

Similarly, there are also no inclusion or exclusion criteria in the proposed study based on race or ethnicity. One of the primary goals of the study is to develop predictive models of glaucoma using racially diverse data. Our goal will be to achieve ~50% enrollment with patients who do not identify as white. Based on preliminary studies, this should be possible for all aims of the study. For *All of Us,* the public data browser shows that 53.49% of participants thus far have identified as “White,” with the remainder identifying as “Black, African American, or African,” “Hispanic, Latino, or Spanish,” “More than one race/ethnicity,” “Asian,” or “Other.” Similarly, during preliminary studies at UCSD to develop predictive models of glaucoma progression based on EHR data, more than one-third of the study cohort (which was based on patients presenting for routine office visits) consisted of racial/ethnic minorities. The glaucoma clinics at UCSD provide care for >3,000 African American patients and >4,000 Latino patients annually. Furthermore, UCSD has dedicated longitudinal research cohorts dedicated to individuals of African descent (the African Descent and Glaucoma Evaluation Study, ADAGES). Given the diversity of the surrounding region, and the demonstrated track record of recruitment of minorities for clinical research, we will be able to successfully recruit minority patients for this study in Aims 2 and 3.

2. Inclusion of Children

Children (individuals under 18) will not be included in the proposed study. The rationale for this decision is because glaucoma that presents in children (infantile/congenital or juvenile glaucoma) are considered separate distinct entities from ocular hypertension and primary open-angle glaucoma that develops in adults. The childhood glaucomas are primarily driven by genetic and anatomic abnormalities, which are generally not present in adults. Because ocular hypertension and primary open-angle glaucoma are virtually exclusively age-related diseases of adulthood, children will be excluded from the study.

RECRUITMENT AND RETENTION

Recruitment and retention activities do not apply to Aim 1 of the study, because it entails a secondary analysis of existing data (retrospective study) from the *All of Us* research program and does not entail any prospective data collection for newly enrolled patients. The remainder of this document pertains to Aims 2 and 3 of the proposal, which will investigate the roles of home blood pressure monitors (Aim 2) and flexible electronic medication adherence sensors (Aim 3) in predicting glaucoma progression.

Recruitment:
Study participants will be recruited during the study period in conformance with the UC San Diego's Human Research Protection Program Guidelines. Patients are solicited for participation in the study by Sally Baxter, MD, [redacted] and other clinicians at UCSD during their clinical evaluation and/or during their existing study visits for the Diagnostic Innovations in Glaucoma Study (DIGS) or the African Descent and Glaucoma Evaluation Study (ADAGES). It is clearly stated in the verbal presentation and on the consent form that this is a voluntary research project and failure to participate will in no way influence the care the subjects will receive. Written informed consent from the patient participant is obtained by a staff research associate, after explaining the objectives of, and procedures involved in this investigation. This explanation includes definitions or descriptions of all specific terms related to glaucoma, such as intraocular pressure and optic nerve.

The research team will follow all the informed consent guidelines of our IRB. Before approaching patients for enrollment, permission will be obtained from the attending ophthalmologists/physicians. Study coordinators will use IRB-approved and HIPAA-compliant procedures to identify potential candidates for enrollment utilizing the inclusion and exclusion criteria per our protocol. During the informed consent process, the following techniques will be employed:

- Study staff (supervised by Dr. Baxter) will describe the proposed study protocol in lay terminology.
- Emphasis will be made that the data collected will be for research purposes and refusal to participate in the investigation will have no effect on the subjects' treatment at a UCSD Health System facility.
- Subjects will be informed that there is no obligation to participate in the study.
- Staff will provide a clinician's name (e.g. Dr. Baxter) and contact information for further questions.
- The subject will be provided with a written copy of the consent form and ample time to have questions answered prior to enrollment.

***Retention*:**
Aim 2 (use of smartwatch-based home blood pressure monitors) entails a short study period of 1 week. Retention will be enhanced by phone calls to participants from research coordinators within the first 2 days of monitor distribution, to ensure adequate use and to evaluate if there are any questions to address. Retention of patient data from the follow-up visit will be enhanced by providing the option to complete the follow-up questionnaire online and to return the blood pressure monitor to UCSD via certified mail.

Aim 3 (validation of glaucoma medication adherence sensors) entails a study period of 6-10 weeks. Research coordinators will call patients 1 week after initial enrollment to check in with the patients, ensure they still have their medication bottles, and offer the opportunity to ask any questions. The patients will be called again 1 week before their follow-up visit to remind them of the date and time of their follow-up. Additionally, patients will be reminded to bring their eye medication bottles with them to the follow-up visit.

As much as possible, study visits will be timed to coincide with the patients' existing study visits from DIGS or ADAGES at the UCSD Hamilton Glaucoma Center or with existing clinical appointments at the UCSD Shiley Eye Institute in order to minimize additional time and transportation burden. Each patient will receive a participation incentive payment of [redacted], the distribution of which can be divided between the enrollment visit and the follow-up visit to enhance study completion/retention. After the study, information stored in the study database will be stored for an indefinite period of time for future reference, including use in subsequent data analyses.

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	University of California San Diego (La Jolla, CA)

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ○ Yes ● No

Enrollment Location Type* : ● Domestic ○ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): University of California San Diego (La Jolla, CA)

Comments: Aim 1 will utilize an existing domestic dataset (All of Us Research Program). Aims 2 and 3 will involve active patient enrollment at UCSD. Planned enrollment table below reflects total enrollment for Aims 2 and 3 of the study.

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	3	2	0	0	5
Asian	12	9	0	0	21
Native Hawaiian or Other Pacific Islander	3	2	0	0	5
Black or African American	15	12	10	8	45
White	45	30	10	8	93
More than One Race	9	6	10	6	31
Total	87	61	30	22	200

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	protection_HumanSubjects.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	○ Yes ● No ○ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	○ Yes ● No
3.5. Overall structure of the study team	

PROTECTION OF HUMAN SUBJECTS

1. Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

Overall Study Design: This study entails three aims: (1) predictive modeling using existing data in the *All of Us* research cohort; (2) evaluating associations between markers of glaucoma progression with blood pressure data generated by smartwatch-based home blood pressure monitors; and (3) measuring glaucoma medication adherence patterns using flexible electronic sensors embedded onto eye medication bottles. Aim 1 involves retrospective analysis of an existing dataset. Aims 2 and 3 involve active recruitment of human subjects.

Eligibility Criteria:

- **Aim 1**: Adult (18 years and older) patients diagnosed with glaucoma (based on SNOMED concept coding, qualifying ICD diagnosis codes, treatment with glaucoma medications, or history of glaucoma-related procedure) included in the NIH-sponsored *All of Us* Research Program study cohort.

- **Aim 2**: Participants will be recruited from the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES) cohorts at the UCSD Shiley Eye Institute and UCSD Hamilton Glaucoma Center. All participants must be 18 years old or older. Participants will be required to have at least one eye with open angles, best corrected visual acuity of 20/40 or better to be included. Participants taking a medication known to affect visual field sensitivity and eyes with a history of intraocular surgery (except uncomplicated glaucoma and cataract surgery), a secondary cause of elevated intraocular pressure, a coexisting intraocular disease affecting visual field, or a problem other than glaucoma affecting color vision may be excluded. Additional exclusion criteria include wrist circumference less than 5.3 in (13.5 cm) or greater than 8.5 in (25 cm), or cognitive or physical impairment that precludes the use of a wristwatch device.

- **Aim 3**: Eligibility criteria are the same as for Aim 2. Additional criteria specific to this aim include: currently self-administering eye medications and ownership and regular use of a smartphone device. Additional exclusion criteria: Anticipation of discontinuation of topical IOP-lowering medications during the period of sensor-based monitoring; cognitive and/or physical impairments that preclude self-administration of eye drops or smartphone use.

For all 3 aims, there are no eligibility criteria based on gender, race, or socioeconomic status. Pregnant women will not be specifically excluded from the study. Other vulnerable populations, such as fetuses, neonates, prisoners, children, groups with known cognitive impairment, and institutionalized individuals will not be involved in the study.

Subject Populations:

- Aim 1: Patient data from the *All of Us* Research Program, which will be accessed via the *All of Us* Researcher Workbench through a data use agreement.

- Aims 2 and 3: Eligible patients seen at the UCSD Shiley Eye Institute who have already been enrolled in the DIGS or ADAGES study cohorts.

b. Potential Risks

Research procedures are detailed in full in the Research Strategy. Components that include human subjects interaction and acquisition of data include: (1) secondary analysis of existing data from *All of Us* participants, (2) collection of smartwatch monitor-generated blood pressure data and electronic sensor-generated adherence data, (3) review of clinical data from the electronic health record (EHR) and from existing clinical research databases (i.e. for DIGS and ADAGES) for development of predictive models, (4) completion of surveys regarding participants' experience with devices involved in the study, and (5) possible undertaking of a human-centered design process to iterate the prototypes for adherence sensors. This study does not entail any changes to the medications, surgeries, or other interventions or treatments relating to the direct clinical care of the patients.

The analysis of data from *All of Us* should not present any risk to participants, because identifiers will have already been removed from the data by the *All of Us* program prior to extraction and analysis by my research team. Risks from participating in the remaining study components will be relatively low risk. Potential risks from using the home blood pressure monitors include wrist or arm discomfort from wearing the smartwatch device and disruption during sleep due to nighttime blood pressure measurements. However, because smartwatch devices have become widely adopted and well tolerated in the general community, we anticipate these risks to be very low. Use of the medication adherence sensors will not require any additional effort from the patient. Participation in surveys and/or design workshops may result in fatigue; however, we have found that people enjoy sharing their experiences and generally like to participate. The use of patient data from the EHR or from existing clinical research databases may result in loss of confidentiality, which may subsequently lead to risks to employability, insurability, and other social risks.

2. Protection Against Risks

a. Recruitment and Informed Consent

Study participants will be recruited during the study period in conformance with the UC San Diego's Human Research Protection Program Guidelines. Patients are solicited for participation in the study by clinicians during their clinical evaluation or during their DIGS/ADAGES study visits. It is clearly stated in the verbal presentation and on the consent form that this is a voluntary research project and failure to participate will in no way influence the care the subjects will receive. Written informed consent from the patient participant is obtained by a staff research associate, after explaining the objectives of, and procedures involved in this investigation. This explanation includes definitions or descriptions of all specific terms related to glaucoma, such as intraocular pressure and optic nerve.

b. Protections Against Risk

Risks associated with smartwatch device wear will be mitigated by appropriate training and education of the participant by the research coordinator at the time of the enrollment visit. Use of the medication adherence sensors do not require any additional effort from participants. The risks of loss of confidentiality will be minimized by limiting access to the data to only key research personnel, using only study identification numbers (instead of medical record numbers, names, or other identifiers) in data that is exported for analysis, and using secure platforms such as REDCap and the UCSD DBMI's HIPAA/FISMA-compliant server alongside additional encryption and password protection on individual data files. All key personnel who will have access to this data will have completed UCSD certifications for human subjects research and HIPAA certification. These measures will minimize the risk of loss of confidentiality.

3. Potential Benefits of the Proposed Research to Research Participants and Others

For Aim 1, participants in *All of Us* will not derive any direct benefit from this study, as their identifiers will have been removed prior to the analysis. However, patients in general may benefit if the predictive

model is able to better characterize the contribution of systemic vascular attributes to the risk of developing or worsening glaucoma. This would improve understanding of the pathophysiology of glaucoma and may uncover potentially new therapeutic targets that could ultimately improve visual outcomes for future patients.

For Aim 2, some participants may discover they have elevated blood pressure using the smartwatch-based home blood pressure monitor that was previously undetected. If they pursue medical treatment for their blood pressure which ultimately decreases their risk of subsequent complications, that is a benefit to them. However, there may be subjects who do not derive any direct benefit from the study – for instance, if they do not have abnormalities in blood pressure regulation, or if they are already being adequately treated for blood pressure issues. Again, on a broader scale, patients in general may benefit if blood pressure monitors are found to improve risk stratification for glaucoma progression.

For Aim 3, participants may benefit by obtaining feedback about their medication adherence, which may encourage them to improve their adherence and thereby reduce their risk of glaucoma progression and subsequent vision loss. They may also uncover insights about their barriers and facilitators to medication adherence, which may not only inform their ability to adhere with glaucoma medications, but may also apply to their ability to adhere with other medications as well. Subjects participating in the prototype design portion of the project will benefit by optimizing their future use of the platform.

4. Importance of the Knowledge to be Gained

Understanding whether data from EHRs, home blood pressure monitors, or electronic medication adherence sensors can assist in the identification of patients at elevated risk of glaucoma progression will advance our knowledge of what benefits may be offered by health IT tools for risk stratifying and monitoring patients with glaucoma. This knowledge will be crucial for future planning of interventions aimed at improving glaucoma outcomes and promoting better vision for these populations. The potential benefits of developing strategies for preventing debilitating vision loss far outweigh the low amount of risk entailed in this study.

Section 4 - Protocol Synopsis (Study 1)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ❍ No

4.2.e. Intervention Model

4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			