Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** The Trustees of the University of Pennsylvania

2. **Reporting Period (start and end date of grant award period):** 6/1/2010-5/31/2014

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Dwight Stambolian MD, PhD

4. **Grant Contact Person's Telephone Number:** 215-898-0305

5. **Grant SAP Number:** #4100051726

6. **Project Number and Title of Research Project:** Improving Vision and Preventing Visual Impairment in Rural Amish and Urban African Americans

7. **Start and End Date of Research Project:** 6/1/2010-5/30/2014

8. **Name of Principal Investigator for the Research Project:** Dwight Stambolian

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 4,604,682.37

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort YR.1	% of Effort YR.2	% of Effort YR.3	% of Effort YR.4	Cost
Aguirre, G.	Investigator	14%	20%	20%	3.4%	120,004.23
Allgyer, S.	Coordinator	17%				77.53
Appel, Sarah	Optometrist	11%	11%			28,480.00
Au, Elizabeth	Technician	45%	37%			39,130.20
Bak, Anna	Coordinator	42%				542.49
Baugh, Kaylene	Coordinator	100%	100%			329.04
Beiler, Anna	Coordinator	100%				115.05
Benjamin, Dony	Student	81%				5,718.11
Benson, N.	Post Doc Fellow	100%	100%	100%	100%	153,406.21
Boxley, S.	Coordinator	100%	100%	100%	100%	266,255.11
Brainard, D	Investigator	8.33%	8.33%		8.33%	36,539.80
Brandes, L.	Res. Specialist	50%				17,601.70
Broussard, C.	Programmer	12.5%				23,513.65
Brown, C.	Coordinator	45%				1,069.58
Butt, Omar	Research Fellow	25%	29%	29%	14%	28,675.09
Chronister, C.	AMD Investigator		0%	10%		541.00
Cideciyan, A	Investigator		5%	1%	1%	13,562.63
Ciner, E.	Investigator	25%	23%	11%	10%	93,365.00
Dana, Nicholas	Student		35%	100%		4,309.02
Dauber, Joanna	Coordinator				6%	659.13
Draper, E.	Optometrist	15%	13%			22,223.00
Ellenberg, Jonas	Investigator	6.4%	7%	7%	5.8%	68,263.49
Engle, Erin	Coordinator	90%	90%	90%	90%	160,840.00
Esch, Mary	Coordinator	60%	17%	100%		919.70
Esch, Sarah	Coordinator	40%				482.72
Estricher, Jackie	Coordinator	8%	36%			10,699.62
Feng, Rui	Investigator	9.9%	8%	15%	20%	79,422.43
Fennelly, J.	Coordinator		4%			174.99
Feinstein, C.	Coordinator		10%			4,630.00
Fisher, Sarah	Coordinator			100%		312.65
Fox, Allison	Coordinator		30%	10%		3,626.28
Fredericksen, N	Student		100%			4,080.16
Gardner, S.	Temple	2%	3%	1.6%		3,058.60
Goldberg, J.	Post Doc		41%			12,788.78
Graboyes,Marcy	Social Worker	13%	13%			24,664.00
Guidiseva, V	Technician	25%	25%	25%	18%	47,710.53
Gupta, Omesh	Professor	8%	8%			7,533.33
Hall, Laura	Coordinator	100%	100%	100%	100%	209,493.48
Haller, Julia	Investigator			1%	1%	768.07
Hender, S.	Coordinator			2.7%		5,427.00

Henderer, J.	Investigator	4%	8.5%	2%		23,374.51
Hoe, Kathleen	Coordinator		100%	2%		252.75
Horst, Violet	Coordinator	58%				12,211.80
Huang, W.	Post Doc	33%	37%	9%	16%	32,627.35
Jacobson, S.	Investigator	12%	10%	1%	12%	77,594.48
Jiang, Yingda	Graduate Student			16.67%	100%	46,401.14
Kazmierkiewicz	Application developer		77%	100%	100%	147,400.41
Kidwell, Kate	Programmer			7.5%		250.94
Kim, Mijin	Research Specialist	50%	50%	50%	50%	110,666.54
King, Sylvia	Coordinator	23%	72%			365.17
Liu, Chrissy	Coordinator	22%				540.32
Luo, Jun	Coordinator	17%				1,095.93
Luo, Xunda	Post Doc		24%	10%	13%	25,018.02
Mackay, Tine	Coordinator	57%	12%			12,640.73
Metzler, Carl	Driver	100%	100%	100%	100%	11,831.15
Nakano, P.	Coordinator	37%	30%	32%		35,803.49
Nwachuku, E.	Student	100%				4,497.70
O'Brien, B.	Phlebotomist	100%	84%			43,124.00
Olivares, M.	Coordinator	19%	24%		6%	22,706.13
Perlino, C.	Retinal Specialist		1%			314.00
Rohrer, Y.	Coordinator	100%	81%	100%	100%	10,820.82
Russell, Robert	Coordinator	18%	18%	3%		21,700.93
Sadigh, Sam	Post Doc		33%	13%	14%	23,525.19
Shao, Hanjuan	Research Specialist				15%	1346.34
Sheplock, R.	Coordinator				.5%	187.49
Shoge, R.	Optometrist	5%	5%			12,016
Soni, Poorva	Programmer Analyst	100%	100%			157,185.11
Stambolian, D.	PI	23%	23%	23%	23%	223,739.53
Stoltzfus, K.	Coordinator	59%	100%	100%		2,556.19
Sumaroka, A.	Data Base Mgr.	13%	8%	2%		20,342.70
Swider, M.	Coordinator		15%	9%	6%	21,222.44
Wolfe, Sharon	Coordinator	3%	17%	3%	5%	29,262.01
Thomas, J.	Temple		17%			341.01
Wagner, Sarah	Coordinator	100%				44,765.00
Weeks, D.	Investigator	10%	9%	15%	2.5%	65,213.11
Willis, Mary	Coordinator		69%	63%		58,380.00
Wolfe, Sharon	Coordinator		17%			17,832.13
Wong, S.	Temple		8%	8%		4,203.79
Yee, Stephanie	Research Specialist	100%	42%			71,751.82
Zook, Emma	Coordinator	100%				447.71

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant,

Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Orlin, A.	Investigator	10%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
Eye Tracker	Focal Point for Contrast Sensitivity	29,950.00
Minus 80 degree Freezer	Store Patient DNA Samples	9,774.97
Topcon Fundus Camera	Photograph Patients	21,995.00
Canon Fundus Camera -	Photograph Patients	29,295.00
18.3 cu ft ultralow temp freezer -	Sample storage	8,620.25
GeneAmp(R) PCR System 9700, Dual 384-Well Sample Block Module	Gene amplification	12,837.16
Mac Pro 12-Core Computers	Data Analysis	15,008.00
Sure Select XT Custom MP3 100 reaction	Sequencing	31,159.00

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes___X_____ No_____

If yes, please describe your plans: Will apply for NIH funding.

12. **Future of Research Project.** What are the future plans for this research project?

Continue the analysis and publish manuscripts.

13. **New Investigator Training and Development**. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male	2			1
Female	2		1	
Unknown				
Total	**4**	**0**	**1**	**1**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic	0		0	0
Non-Hispanic	4		1	1
Unknown				
Total	**4**	**0**	**1**	**1**

	Undergraduate	Masters	Pre-doc	Post-doc
White				1
Black	4			
Asian			1	
Other				
Unknown				
Total	**4**		**1**	**1**

14. **Recruitment of Out-of–State Researchers**. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No___X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes____X_____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

Provided a central pool of money to bring investigators together to analyze Age-related Macular Degeneration in African Americans.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No____X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No_____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No___X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.
List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims <u>for the period that the project was funded (i.e., from project start date through end date).</u> Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons

why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

The overall goal of this project is to investigate the genetic and environmental determinants of Visual Impairment, to develop new methods of treatment to delay its progression, and enhance the use of remaining residual vision. In particular, this proposal will focus on Age-related Macular Degeneration (AMD), which is the leading cause of Visual Impairment in Pennsylvania. The research aims are to (1) enhance vision rehabilitation for African Americans with central visual impairment, (2) determine the genetic and environmental modifiers in AMD, (3) determine visual cortex function in response to the central visual deficit seen in AMD, and (4) identify the barriers for minorities that prevent access to vision care.

The objectives of this project are to assess methods for improving treatment of visual impairment for Age-Related Macular Degeneration; determine the genes associated with Age-Related Macular Degeneration in African Americans; phenotype Amish and African American subjects with Age-Related Macular Degeneration to determine characteristic retinal signs associated with genetic risk variants; assess dietary supplementation to enhance macular pigment density; determine the extent of cortical plasticity in advanced Age-Related Macular Degeneration; and, identify disparities in vision care within the African American community.

To address the need for enhancing vision rehabilitation, a clinical trial will be performed comparing home vs. office-based rehabilitation in African American subjects with visual impairment to determine if there is an advantage of one method over another. To assess the genetic and environmental modifiers in AMD, African American and Amish case/controls will be genotyped for risk variants and phenotyped for retinal changes with advanced imaging technology. To address the need to understand visual cortex function in AMD subjects with central visual deficits, subjects will undergo extensive testing with functional MRI to determine if there has been any remapping and shift of visual cortical responsiveness. To identify the reasons for minorities having poor access to vision care, faculty at Lincoln University in collaboration with other faculty participating on this RFA, will develop and test a study protocol to identify the hurdles that impede access to vision care in African American youth and their parents.

Specific Aims

Age-Related Macular Degeneration (AMD) is the major cause of blindness and visual impairment in the elderly. The incidence of AMD is rising dramatically as people live longer and gain more years of productive life. Overnight, however, the benefit of increased longevity can be lost by the negative effects of this visual impairment. When people lose their central vision to AMD it becomes difficult to read, drive, recognize faces – they lose their independence. **The specific aims of this proposal address both present and future needs of individuals with AMD.** A present need for severely affected patients with central visual deficit, caused by AMD and other ocular diseases, is access to rehabilitation of their residual vision. Minorities, especially, need better access toward improving quality of life. To address this we propose to investigate alternative methods to enhance the use of residual vision in African Americans which could improve vision for daily activities (**Aim 1**). The future in AMD is prevention of progression from early disease to later blindness. We now know that individuals can be at high-risk to progress to visual loss based on genetic susceptibility and environmental risk factors. To address this we propose to identify modifiable risk factors and target subjects with these risks using interventions to reduce the risk factors (**Aim 2**). The future of visual rehabilitation will be served by understanding the brain's response to retinal disease so that strategies can be developed to take advantage of this altered response (**Aim 3**). Lastly, to insure that this investment in both understanding and progress for AMD patients will continue beyond the project period, educational and community outreach programs will be established (**Aims 1 and 4**). Hypotheses and specifics related to these aims are given below.

Aim #1. Vision Rehabilitation Research for African Americans with Central Vision Impairment (VISRAC)" Study

The primary treatment for severely reduced vision (low vision) caused by AMD and other ocular diseases is vision rehabilitation, which has been shown to improve quality of life and patient independence. The purpose of this aim was to increase access to essential vision rehabilitative services and improve vision outcomes for older African Americans (AAs) with central vision impairment who often receive inadequate care even though opportunities for this type of intervention are available. Our approach to this problem was to compare home-based vision rehabilitation to office-based vision rehabilitation of AAs with advanced retinal disease. At the start of the study, we hypothesized that increased awareness of the home environment, more

accurate appraisals of patient context or goals and better application of environmental modifications should result in an easier transfer of learned skills to recommended home practice activities, increased compliance and improved likelihood of successful outcome. We planned to enroll 60 AA subjects with central VI into the VISRAC study to achieve an effective sample size of 48 after dropout.

METHODS

Identification of Potential Study Subjects: Individuals were recruited over a three year period from December 2010 through October 2013 and were identified through prospective and retrospective chart review of patients at The Eye Institute of the Pennsylvania College of Optometry, as well as referrals from external eye care providers and agencies.

Determination of Eligibility:
Potential Study subjects underwent an Initial Eligibility Interview (IEI) followed by a Clinical Eligibility Exam (CEE). This enabled a more stream-lined identification of study subjects, allowing consideration for their time and resources. The following criteria were used to determine eligibility either at the time of the IEI or during the CEE. Inclusion criteria: (1) availability of eye exam records from within one year, (2) Visual acuity (VA) at the last exam in the range of 20/70-20/400, (3) central visual field defect (4) no past home based vision rehabilitative (VR) services, (5) $\geq$ 40 years of age and self-identification as AA, (6) willingness to have home visits. Exclusion criteria included: (1) significant peripheral visual field loss (to less than 20 degrees diameter) in the eye used for reading, (2) an eye movement disorder that interfered with reading (e.g. nystagmus), (3) uncorrectable diplopia, (4) planned or scheduled medical or surgical treatment requiring a recovery > 2 weeks during study period, (5) planned or scheduled medical or surgical treatment to improve vision during study period (e.g. cataract extraction; anti-VEGF therapy), (6) Low vision (LV) instruction within previous 24 months, (7) unwillingness to complete LVRT within 90 days of enrollment, participate in phone interviews or allow home visits during daytime hours. Subjects meeting IEI criteria proceeded to the CEE that was conducted by a study optometrist at The Eye Institute. Written Informed Consent was obtained for all participants. The VISRAC Study was approved by the Salus University Institutional Review Board.

The Clinical Eligibility Exam included distance Early Treatment of Diabetic Retinopathy (EDTRS) VA, visual field measurements, refraction, binocular assessment, ocular motor evaluation and an ocular health evaluation.

The VISRAC study was implemented in 5 visits over a 2 to 3 month period. Visits 1, 3 and 5 were performed in the clinic. VR (visits 2, 4) took place either in the home or clinic. Significant effort toward retention was made by the Study Coordinator (SC) to maintain contact, encourage compliance, facilitate transportation, optimize scheduling and answer questions. The SC and PI were available to answer procedural questions throughout the study.

The Certified Low Vision Therapist (CLVT) was masked to the patient's assigned study arm for the instructional hour during the patient's first visit, but was necessarily unmasked during the actual VR. A single CLVT delivered the VR in the two settings, minimizing the impact of different approaches and personality differences. The CLVT follow the protocols as outlined in the Manual of Procedures for the study and following guidelines of the Academy for Certification of VR Professionals to minimize bias. The CLVT, was not be involved in

administration of any outcome measures. The Low Vision Optometrist (LVOD) was masked to the patient's assigned study arm throughout the study.

1st Study Visit: Following written informed consent to participate in the study, subjects were randomly assigned to a treatment arm. The control arm received standard clinic based LVRT while the intervention arm received home based LVRT. The first study visit began with a social service intake by a study social worker (SSW) to assess (1) activities of daily living (primary outcome) (2) ocular, systemic and psychosocial history (3) identification of rehabilitation goals to guide the low vision evaluation (LVE). This was followed by a Low Vision Evaluation (LVE) by the LVOD who provided a prescription of standard optical (e.g. eyeglasses) and low vision (LV) magnification devices to address the subject's rehabilitation goals. All subjects then received one hour of basic instruction in the use of the prescribed devices by the CLVT. Study subjects were provided with appropriate reading practice exercises to use at home prior to the second study visit with the LVRT

Activities of Daily Living. The Veteran's Administration Visual Function Questionnaire (VA LV VFQ-48) was used as the primary outcome measure. Such self-report questionnaires measure the difficulties visually impaired persons have in performing activities of daily living and are recognized as vital to determining successful rehabilitation outcomes. In particular, the VA LV VFQ-48 shows strong test-retest reliability and validity for individuals with moderate to severe vision loss and has the advantage that specific areas of visual function such as reading tasks can be sub-analyzed. This questionnaire is not new to clinical trials and has been used successfully in the Low Vision Intervention Trial (LOVIT).

Visual Acuity. The Ferris-Bailey Early Treatment of Diabetic Retinopathy (ETDRS) Distance VA Chart was used to measure distance VA. This chart was also used to monitor VA changes and to evaluate VA with distance magnification devices.

Components of Initial LVE. Distance and Near VA, Brightness Acuity Test, review of visual fields, assessment of eccentric viewing, refraction, evaluation of ocular alignment and motilities, contrast sensitivity testing, prescription of low vision devices, ocular health and fundus photos.

2nd Study Visit – Vision Rehabilitation One (VR1): The first LVRT visit took place within approximately 2 to 3 weeks of the first study visit in the clinic or at home depending on the patient's assigned study arm. All clinic based LVRTs occurred in a manner to maximize separation from the location of the LVE in order to keep the LVOD and SSWs masked to the subject's treatment arm. VR was provided by the same CLVT for all patients throughout the study. The LV devices and recording forms used by the CLVT were identical for both treatment arms. The LVRT included the following: Visual skills training, Optical Device Instruction, Environmental modifications, use of non-optical devices and management of illumination as outlined in the Manual of Procedures for the study.

3rd Study Visit: This visit took place in the clinic for all subjects within approximately 2 to 3 weeks of their 2nd study visit (VR1) and included a social service update interview by a SSW and a LV reevaluation by the LVOD to monitor changes, assess progress and make necessary modifications.

4th Study Visit - Vision Rehabilitation Two (VR2): The second LVRT visit took place within approximately 2 to 3 weeks of the third study visit in the clinic or at home depending on the patient's assigned study arm. The LVRT was a continuation of recommendations and training from the previous visit.

5th (Final) Study Visit: Subjects were seen at the clinic within approximately 2 to 3 weeks of their 4th study visit. A social service exit interview by the SSW included the re-administration of the primary outcome measure (VA LV VFQ 48), cognitive assessment (to rule out degradation in mental ability) and an assessment of goals and concerns. The LVE by the LVOD included a reevaluation and recommendations or necessary referrals as would be customary in a LVE. The SSW provided referrals for resources including counseling, additional rehabilitative services or medical referrals as needed. The subject's involvement in the study was considered complete at this point.

The primary outcome measures are a comparison of the changes in visual function as assessed using the Veterans Affairs Low Vision Visual Functioning Questionnaire – 48 Item (LV VFQ-48) at baseline and after completing a multidisciplinary rehabilitation program. Statisticians who did primary analysis were blinded to the intervention assignment initially.

To ensure that clinical study personnel could not anticipate the treatment assignment of study participants, a permuted block randomization method with a variable block size of 4 or 6 was used to allocate participants into the intervention and control groups. The randomization was stratified on baseline central visual deficit because this visual finding is the most likely to have an impact on the primary outcome measure. The randomization allocation list was provided on a sheet with two strata, for those with central visual reading below and above 20/200 separately to the Salus study coordinator. The participants were randomized as they completed their eligibility determination.

All analyses were carried out on an intention-to-treat basis. Randomization was checked for balance across central visual reading strata. The demographics and baselines between the intervention and control groups were compared. The comparison between categorical variables, including sex, living situation, housing, general health, education, employment, accompany type, and all components of baseline reading assessment categories was performed using the Fisher's exact test and the comparison of age was performed using two-group t-test. In addition to sex and age, any variable that show imbalance at a significance level of 0.05 between two groups were considered as covariates to be adjusted to evaluate the treatment effect.

Linear regression modes were used to test the difference in the primary outcomes between the two intervention groups, adjusted for the potential confounders mentioned above. All analyses were performed using R version 2.15.3 for Windows (the R Foundation for Statistical Computing).

Results

A total of 245 potential study patients were identified prospectively, retrospectively or through referral. Of these, 76 were determined to be potentially eligible from an Initial Eligibility Interview and willing to undergo an Eligibility Eye Exam. A total of 56 patients were found eligible, enrolled in the study and randomized equally to two treatment arms. Eight patient were withdrawn from the study (attrition rate of 14%), resulting in 48 patients who completed all five visits. Among them, 36 (75%) had baseline central visual reading score <20/200 with 17 and 19 assigned to treatment A and B, respectively, suggesting an effective randomization across baseline strata (Fisher's exact test $p = 0.7389$).

Table 1 summarizes the characteristics of the participants separated by two treatment groups. The patients in treatment B were older than those in treatment A, but the difference is not

significant given the current sample size. There were more females than males in treatment A and equal numbers of two genders in treatment B. The numbers in each category of education level are sparse. Several more patients finished high school and less received college education in treatment A group than treatment B group. The differences in living condition, type of housing, general health status, employment status and companies are not significant between two treatment groups.

Table 2 presents the screening assessment of two treatment groups according to questionnaires. There was minor difference in most items except 8 patients in treatment A can read facial expressions on TV, appliance control knobs/buttons, and price tags at store, while only 1 or 2 patients in treatment B group could do these, suggesting that the group A had better baseline than group B and that such difference should be adjusted in the primary analysis. Therefore, we adjusted for the baseline VFQ-48 score in the primary analysis.

We compared the change in each subcomponents of the VFQ-48 score, i.e., visual ability score, reading score, mobility score, visual information score, and visual motor score from initial 1st visit to the exit 5th visit, adjusted for sex, age, age^2, corresponding baseline score, and baseline $score^2$. Quadratic terms of age and baseline scores were included to reflect the non-linear relations between the score change and age or baseline scores. Table 3 shows the average change of the VFQ-48 sub- and total scores in two treatment groups. Almost all scored were positive, indicating the score improvement from the 1st to 5th visits. Patients in treatment B had significantly more improved the total VFQ-48 score (3.31 points higher) and vision motor score (1.96 points higher) in average than treatment A. The average improvement in visual ability score and reading score are also better in treatment B, yet were not significant at the 0.05 level probably due to the small effect size or shorter follow-up.

Table 1. Demographic Characteristics

	Categories	Treatment A	Treatment B	P
Age		62.958 (14.070)	66.458 (12.803)	0.3721
Sex				0.7721
	Male	10 (41.7%)	12 (50.0%)	
	Female	14 (58.3%)	12 (50.0%)	
Current living situation				0.8554
	Alone	10 (41.7%)	11 (45.8%)	
	W. Spouse	5 (20.8%)	6 (25.0%)	
	W. Child	3 (12.5%)	4 (16.7%)	
	W. Parent	2 (8.3%)	1 (4.2%)	
	W. Relative	1 (4.2%)	0	
	W. Friend	2 (8.3%)	2 (8.3%)	
	Other	1 (4.2%)	0	
Type of housing				1.0000
	Apartment	6 (25.0%)	6 (25.0%)	
	House	17 (70.8%)	17 (70.8%)	
	Rent rooms	1 (4.2%)	1 (4.2%)	
General Health Status				0.9869
	Average	8 (33.3%)	8 (33.3%)	
	Excellent	2 (8.3%)	3 (12.5%)	
	Good	8 (33.3%)	8 (33.3%)	
	Poor	4 (16.7%)	3 (12.5%)	
	Other	2 (8.3%)	2 (8.3%)	
Highest level of education completed				0.2176
	K-6	0	1 (4.2%)	
	8th grade	5 (20.8%)	5 (20.8%)	
	High school	13 (54.2%)	9 (37.5%)	
	GED	1 (4.2%)	1 (4.2%)	
	Some college	0	5 (20.8%)	
	Undergraduate	2 (8.3%)	2 (8.3%)	
	Tech. school	0	1 (4.2%)	
	Adv. degree	2 (8.2%)	0	
Current employment status				0.5210
	Employed	1 (4.2%)	2 (8.3%)	
	Retired	10 (41.7%)	13 (54.2%)	
	Disabled	6 (25.0%)	6 (25.0%)	
	Unemployed	5 (20.8%)	3 (12.5%)	
	Other	2 (8.3%)	0	
Accompanied by				0.7510
	Alone	18 (75.0%)	16 (66.7%)	
	Family	5 (20.8%)	6 (25.0%)	
	Friend	0	1 (4.2%)	
	Other	1 (4.2%)	1 (4.2%)	

Table 2. Assessment at Screening

	Treatment A	Treatment B	P*
Central visual reading score <20/200	17 (70.8%)	19 (79.2%)	0.7389
Read newspapers	11 (45.8%)	6 (25.0%)	0.2270
Read magazines	2 (8.3%)	3 (12.5%)	0.9999
Read standard print books	2 (8.3%)	5 (20.8%)	0.4158
Read large print books	1 (4.2%)	1 (4.2%)	1
Read religious material	8 (33.3%)	11 (45.8%)	0.5556
Read mail/bills	13 (54.2%)	14 (58.3%)	0.9999
Read labels	13 (54.2%)	15 (62.5%)	0.7702
Read print on TV	7 (29.2%)	8 (33.3%)	0.9999
Read facial expressions on TV	8 (33.3%)	2 (8.3%)	0.0723
Read numbers/words on remote control	2 (8.3%)	1 (4.2%)	0.9999
Read controls and print on audiovisual equipment	2 (8.3%)	3 (12.5%)	0.9999
Reading instructions for food preparation	2 (8.3%)	3 (12.5%)	0.9999
Reading appliance control knobs/buttons	8 (33.3%)	2 (8.3%)	0.0723
Reading/writing checks	3 (12.5%)	5 (20.8%)	0.7008
Read time on watch	1 (4.2%)	2 (8.3%)	0.9999
Read buttons on telephone/cell phone	3 (12.5%)	5 (20.8%)	0.7008
Read price tags at stores	8 (33.3%)	1 (4.2%)	0.0226
Read signage at stores	6 (25.0%)	8 (33.3%)	0.7516
Read street signs or bus numbers	8 (33.3%)	10 (41.6%)	0.7661
Glare disturbance when reading inside or identifying signage outside	6 (25.0%)	8 (33.3%)	0.7516
Read print on computer screen	3 (12.5%)	3 (12.5%)	1
Read numbers on playing cards	1 (4.2%)	0	0.9999
Read words on board games	2 (8.3%)	1 (4.2%)	0.9999
Other	1 (4.2%)	0	0.9999

*Fisher's exact test

Table 3. Comparison of primary outcomes VFQ-48 scores between two treatment groups

	Mean Change (95% C.I.) in HB	Mean Change (95% C.I.) in CB	P-value for comparing HB and CB[+]
Change in:			
Visual ability score	0.874***(0.401, 1.347)	1.283***(0.740, 1.826)	0.0570
Reading score	1.924**(0.681, 3.168)	2.018***(1.328, 2.7078)	0.0536
Mobility score	-0.064 (-0.918, 0.790)	0.806 (-0.046, 1.6578)	0.1016
Visual information score	1.271***(0.710, 1.832)	1.249***(0.656, 1.8401)	0.5085
Visual motor score	1.340 (-0.593, 3.2723)	3.300** (1.348, 5.253)	0.0439

[+]Adjusted for age, age^2, sex, baseline values and baseline value$^{2;}$
* 0.01<P<0.05, **0.001<P<0.01, ***P<0.001 for testing significant improvement at the 5th visit compared with baseline.

Aim #2. Genetic and environmental modifiers in AMD

Our hypothesis is that differences in susceptibility to AMD are influenced by [a] age, [b] inherited differences in susceptibility genes, [c] environmental risk factors such as smoking and other modifiable factors, and [d] diet, that secondarily affects nutritional antioxidant status. This predicts that AMD susceptibility is governed by complex gene-environment interactions which may be detected by Single Nucleotide Polymorphisms (SNPs)/Copy Number Variants (CNVs) and lifestyle factors. Current information about genetic and environmental susceptibility for AMD is mostly confined to Caucasians. Few studies have been performed in AAs. This proposal will identify candidate gene SNPs/CNVs that are over-represented in AA cases with AMD compared to AA controls and to utilize modern imaging technology to define the natural history of the early disease features. A subset of patients with central-macular photoreceptor loss at high-risk of developing advanced AMD will undergo a trial of dietary supplementation.

Specifically, DNA will be collected from 400 AA cases and 400 AA controls. Subjects will be genotyped for genes previously shown to be associated with AMD in Caucasians to replicate or refute the significance of these genes in AAs. A cohort of Amish subjects with AMD will be genotyped for the known gene variants previously identified in Caucasians because this cohort is recognized as an underserved community in Pennsylvania and known to have a high prevalence of AMD. AA and Amish subjects with different combinations of SNP variants and early stage AMD disease will have known modifiable environmental risk factors determined (i.e. smoking habits, body mass index, dietary antioxidants). These data will be used to educate and counsel high-risk patients to increase their awareness of the risks and improve medical surveillance of treatable complicating disorders. We propose to evaluate the retinal cell changes in early AMD through enhanced imaging technologies in order to identify early retinal signs that will become

outcome measures in future therapies. Novel assays will be developed for the two macular cell types impacted by AMD: photoreceptors (PR) and retinal pigment epithelium (RPE).

Subaim 2A. Genotyping of Candidate Genes in African Americans
The target for this study was 400 cases and 400 controls.
We collected 427 cases and 397 controls.

Subaim 2B. Genotyping of Candidate Genes in African Americans and Amish
The target for this study was 160 AA and Amish patients.
We genotyped 397 cases and 427 controls.

Genotyping has been completed on all subjects using an Illumina exome chip. Analysis is currently ongoing.

Subaim 2C. Phenotyping of AMD subjects
The target for this study was 160 AA and Amish patients.
We phenotyped 144 AA and Amish patients.

METHODS AND RESULTS

Our goal was to advance understanding of the disease expression of the atrophic form of age-related macular degeneration (AMD) in two populations: rural Amish and urban African Americans using non-invasive methods. Well-known markers for early stages of atrophic AMD are drusen, extracellular deposits between Bruch's membrane (BrM) and the retinal pigment epithelium (RPE). Drusen have been traditionally identified and viewed *en face*, whether by color photography, fluorescein angiography or by clinical examination. Quantifying drusen and other abnormal fundus features by *en face* viewing has been one of the mainstays of classification schemes for AMD and of assessing outcomes of various clinical trials. The microscopic details of drusen have historically been described through postmortem donor retinal histopathology. The advent of optical coherence tomographic (OCT) cross-sectioning of the retina has added a further modality to the armamentarium of non-invasive assessment of the microscopic details of AMD. Our studies of both AMD populations used spectral domain OCT and the data were quantified and analyzed to determine the relationship of drusen and the adjacent photoreceptors. Both sets of results have been published.

Amish patients with AMD

We examined mainly intermediate non-neovascular AMD, defined as the stage demonstrating one or more large (≥125 μm) drusen but without foveal geographic atrophy. In the atrophic form of AMD, histopathological studies have demonstrated photoreceptor loss and in the many published OCT images including drusen and outer neural retina, it is evident that there is an associated thinning of the photoreceptor outer nuclear layer (ONL). Quantitation of the relationship of drusen and photoreceptors has only occurred, however, in a limited number of non-invasive cross-sectional imaging studies. Our analyses focused on this relationship. In the conduct of these studies, we not only confirmed previous findings but also made unexpected novel observations.

First we examined as controls the maculae of normal older (over 50 years old) Amish subjects (; both ONL and the sum of inner and outer segment lengths (IS+OS) were at maximal thickness at the fovea and decreased with increasing eccentricity across the macula. The foveal ONL thickness was 111.3±10.5 µm (mean±SD) consistent with published measures in normal eyes which tend to show thickening with normal aging. At 3 mm eccentricity, ONL thickness was 62.3±4.9, 56.3±3.6, 57.4±4.6, and 58.1±4.5 µm along the superior, inferior, temporal and nasal retinal meridians, respectively. The IS+OS thickness at the fovea was 81.4±3.1 µm, and at 3 mm eccentricity it was 54.0±3.2, 50.9±2.2, 51.0±1.7, and 52.1±3.1 µm along superior, inferior, temporal and nasal retinal meridians, respectively.

In the maculae of the Amish AMD patients, the spatial distribution of the 750 large drusen that we analyzed indicated that the majority of these drusen (442/750; 59%) were concentrated in the foveal and parafoveal region extending to 1.5 mm eccentricity. The distribution of drusen was circularly isotropic and did not favor any specific retinal quadrant. Average width of the drusen was 352 (±153) µm and the average height was 78 (±31) µm. The photoreceptor laminae overlying the drusen were abnormal. ONL thickness measured at the peak height of each druse was compared to location-matched control values, and 689/750 loci (92%) showed significant (>2SD) thinning. On average, the reduction in overlying ONL thickness was 48% of the mean normal value. The extent of ONL thickness reduction was strongly related to maximum drusen height (r^2=0.48, 46% decrease in ONL per 100 µm increase in drusen height).

To investigate further the effects of drusen on outer retinal architecture, we asked whether the reductions in ONL over drusen were accompanied by changes in the photoreceptor IS+OS layer. The IS+OS layer thickness overlying drusen was also reduced and also strongly related to drusen height (r^2=0.46, 38% decrease in IS+OS per 100 µm increase in drusen height). The thickness fractions of ONL and IS+OS overlying drusen were correlated (r^2=0.53) with a linear regression slope of near unity. The great majority of loci (685/750; 91%) showed abnormally reduced ONL and IS+OS thickness. Among the rest of the loci, 58/750 (~8%) showed normal ONL but reduced IS+OS; 4 loci had reduced ONL and normal IS+OS, and 3 loci had both normal ONL and IS+OS thickness. These cross-sectional results suggested that IS+OS disease may precede ONL thinning.

ONL thickness was also measured in regions neighboring drusen to determine whether abnormally reduced photoreceptor laminae were also present in these paradrusen regions without RPE elevation. We first performed an observational study of outer retinal architecture with line scans along the vertical meridian extending 3 mm superior and 3 mm inferior to the fovea in 23 eyes of 19 AMD patients. Of the 23 eyes, 18 had drusen greater than 50 µm in height and served to confirm the observations from the raster scans that ONL thickness was reduced in association with taller drusen. Paradrusen loci in 7 of the 18 eyes showed ONL thickness that was within normal limits. Eleven of the 18 eyes had the surprising finding of increased thickening of the ONL at paradrusen regions. Five of 23 eyes had no drusen that were greater than 50 µm in height. ONL thickness above these smaller drusen (or edges of larger drusen not captured in the scan) was within normal limits. Paradrusen loci were also within normal limits for ONL thickness, for the most part, with the exception of two eyes which showed one or several regions with abnormally thickened ONL compared to the limits (mean+2SD) in aged normal eyes.

The surprising observation of thickened ONL on vertical profiles through the central retinas of AMD patients prompted us to extend our analyses away from the midline to raster scans covering the macula in two dimensions. We quantified photoreceptor thickness at paradrusen areas (738 loci) that were qualitatively selected to have normal-appearing laminar

architecture without RPE elevation as close as possible to previously identified drusen in 63 AMD eyes. ONL and IS+OS measurements at paradrusen locations mimicked the analyses we had performed over drusen. Nearly three-fourths of paradrusen loci (527/738; 71.5%) showed ONL that was within the normal limits. Some of these paradrusen areas, however, showed substantial thinning of the ONL (67/738 locations; 9%) when compared to location-matched normal limits. Further, we found paradrusen areas that had significant thickening of the ONL (144/738 locations; 19.5%) when compared to location-matched normal limits. The latter measurements confirmed and extended the observations in the vertical profiles.

There was no spatial pattern of distribution for these paradrusen changes in ONL. Paradrusen locations with thickened ONL, normal ONL, as well as locations with decreased ONL were found at all eccentricities measured. The distance between paradrusen locations with thickened ONL and the locus of peak height of their neighboring drusen (311±135 µm) was not different than the distance at normal (302±119 µm) or thinned (313±188 µm) paradrusen locations. There were no obvious clinical features that distinguished eyes (n=38) with evidence of thickened ONL loci from the entire cohort of intermediate AMD eyes we analyzed: 18% of the eyes with thickened ONL versus 16% of all AMD eyes had intraocular lenses; median spherical equivalent refraction (in the subset of patients with natural lenses) was 0.25D in eyes with thickened ONL versus plano in all intermediate AMD eyes (range was identical: -3.25 to +4.00D); and median age and range of ages were identical (median 74, range 53-83 years) in eyes with thickened ONL versus in all eyes.

To understand whether ONL thickening was only associated with paradrusen regions or if it could also be observed distant to drusen, we quantified photoreceptor parameters in a subset of 32 AMD eyes at the boundaries of the 6x6 mm macular raster scans where drusen were more rarely found. Specifically, 16 loci (at eccentricities of 3 to 4.24 mm) were sampled in each eye and compared to normal limits. Nine of 32 eyes (28%) showed one or more loci with abnormally thickened ONL at these pericentral locations. For a subset of 4 AMD patients with pericentral ONL thickening and 2 patients without such evidence, high resolution maps of ONL topography and thickness differences from normal controls were generated to better understand the spatial extent of the regions both near and distant to drusen that showed changes in ONL thickness. Results from these 6 AMD patients were as follows. A 78-year-old patient with 13 large drusen peaks (average elevation, 85 µm) distributed in the parafoveal region showed delimited regions of paradrusen ONL thickening. Maximum ONL thickening was 7.5 µm above normal limits. Most of the paradrusen regions and all of the perifoveal region distant from drusen had ONL thickness within normal limits. A 76-year-old patient also with 13 large drusen peaks (average elevation, 113 µm) in the parafoveal regions showed ONL thickening at the foveal region as well as many paradrusen regions. Maximum ONL thickening was 34 µm above normal limits. A 79-year-old patient with 23 large drusen peaks (average elevation, 79 µm) in the perifoveal regions showed ONL thickening in paradrusen regions as well as in regions more distant to drusen. Maximum ONL thickening was 16 µm above normal limits. An 82-year-old patient with 19 large drusen peaks (average elevation, 70 µm) in the para- and perifoveal regions showed some paradrusen thickening as well as thickening distant to drusen. Maximum ONL thickening was 12 µm above normal limits. A 74-year old patient with 7 perifoveal drusen (average elevation, 72 µm) and an 81-year-old patient with 17 para- and perifoveal drusen (average elevation, 89 µm) showed extensive regions of ONL thickening distant from drusen. Maximum ONL thickenings were 16 and 20 µm above normal limits, respectively. These examples in a subset of

intermediate AMD eyes demonstrate that ONL thickening is detectable in the immediate vicinity of large drusen as well as distant to drusen.

To summarize, our results of quantifying photoreceptor structure by OCT in a cohort of Amish AMD patients confirm and extend previous findings in other populations. As expected there was decrease of the thickness of photoreceptor lamina above drusen, but we showed for the first time that the decrease of photoreceptor lamina was linearly and quantitatively predicted from drusen height. Recognizing that OS shortening is an early feature of hereditary retinal degenerations, we determined the relationships with drusen of the IS+OS and ONL laminae separately. The IS+OS layer was reduced over drusen, as has been previously reported. Of interest, a minority (~8%) of loci showed reduced IS+OS but normal thickness of ONL, possibly indicating a disease sequence although serial data will be required to clarify this. Reductions in IS+OS were directly proportional to reductions in ONL, a finding consistent with results in animal models of retinal degeneration in which there have been demonstrations of proportional rod outer segment shortening and ONL loss by histopathology.

What do our OCT results of ONL and IS+OS reduction above drusen mean? Histopathological studies of postmortem eye donor tissue indicate varying degrees of photoreceptor cell loss overlying drusen. Rod and cone IS and OS have been shown to be distorted by the protruding drusen and OS are shortened. As we found non-invasively, the abnormalities in photoreceptor IS and OS in donor retinas have been reported to be related to drusen size, both height and width. What is not known is whether our findings at a single timepoint showing reduced photoreceptor parameters are indeed the *in vivo* correlates of the single timepoint histopathology that shows similar results. There is a temptation to relate the two data sets, but the literature on AMD pathogenesis and progression suggests that the connection may not be so simple. Regression of drusen is known to occur from *en face* fundus studies and has been documented by OCT. Although not specifically addressed or measured, some published images of serial OCTs in AMD show that ONL which is reduced overlying drusen at one timepoint may increase to more normal-appearing thickness at a later time. Obviously needed are further longitudinal OCT data measuring photoreceptor parameters as well as drusen parameters. There is no doubt that photoreceptor degeneration occurs in AMD and that drusen are harbingers of the disease, but the exact disease sequence requires clarification so that clinical trial results are not misinterpreted when a treatment is associated with OCT change that may simply be part of the natural history.

How can a dynamic ONL reduction with reversal be explained? Among the proposed pathogenic processes resulting from protruding drusen is physical displacement of ONL and IS+OS. This is unlikely to be without later consequence and may be one of many components of cumulative photoreceptor stress. Other suspected mechanisms for photoreceptor degeneration beyond the compressing effects of drusen include drusen-induced impairment of metabolic exchange from RPE and choroid, and activation of the immune system with negative sequelae.

The ONL measurements in paradrusen locations indicated that most fell within the normal limits of locus-specific older control data. Other regions adjacent to large drusen had significantly reduced ONL thickness. Why would there be thinned ONL in areas with no overlying drusen? One explanation is that a diffuse degenerative process ensues in AMD and results in photoreceptor losses regardless of its relationship to drusen. Histopathological studies have shown that widespread photoreceptor loss can be present in AMD. Alternatively, regressing drusen can lead to degeneration of the RPE and photoreceptor layer and result in geographic atrophy. Drusen have a dynamic nature and can spontaneously shrink or regress at times. Focal

patches of atrophy left by the fading of most drusen, as well as generalized drusen related atrophy, have been described.

An unexpected finding was that there were regions of ONL thickening neighboring large drusen. With topographic mapping in a subset of patients, the thickening was not limited to paradrusen loci in the central macula but could also be found near the peripheral edges of the macula distant from drusen. The magnitude of thickening we measured in intermediate AMD patients could extend 8-34 µm beyond the age- and race-matched normal limits. Our results suggest that the photoreceptor disease in AMD is more complex than a localized loss of photoreceptors due to drusen. Several hypotheses could explain the finding of thickened ONL. One possibility is that chronic degenerative stress is causing hypertrophy of Muller cell processes which extend through the ONL and cause thickening, before overt atrophy ensues. A basal level of photoreceptor stress may exist with normal aging which has been speculated to contribute to the thickening of the foveal ONL observed with age. It is of interest that in late stage AMD with geographic atrophy and foveal sparing there can be thickening of the residual foveal ONL; this has been postulated to result from a pre-apoptotic stage. In other retinal degenerative conditions, such as retinitis pigmentosa (RP), one of the earliest disease features that appear before degeneration is Muller cell hypertrophy in stressed retina. Local injury, in the form of cell loss, has been shown to provoke a Muller cell reaction as a response to neuronal insult. Muller glial reaction after laser photocoagulation in the mouse retina, for example, has been demonstrated. Laser injury stimulated local Muller cell activation and directed migration of nuclei into the ONL. This type of Muller cell migration could potentially contribute to the ONL thickening that we observed. Paradrusen regions with photoreceptor layer thickening may be caused by degenerative stress, which has been suggested to represent the earliest signs of photoreceptor loss, and a phase that precedes degeneration. Several studies have observed increases in photoreceptor layers in retinal degenerative diseases and a hypothesis has been that these represented early signs of retinal stress. Alternatively, photoreceptor stress and cell loss can result in increased levels of growth factors, leading to thickening of the ONL surrounding the drusen. Finally, the wealth of new information about activation of the immune system and the evidence for a role of inflammation in early AMD prompts the question of how this may relate to our finding of thickened ONL in the current study. The exact sequence from activated inflammasome to the photoreceptor layer effects we observed is not known but worth exploring in detail, especially if the photoreceptor effects are markers for early disease in retina away from drusen.

Our findings can also yield insight into why studies measuring localized function in retinal regions with drusen have not yielded results with a clear consensus. Some studies found a similar sensitivity loss in drusen versus non-drusen areas; others found lower sensitivities in drusen versus non-drusen areas; and others found decreased sensitivity in some drusen areas (compared to non-drusen areas) but not in others. Our *in vivo* anatomical findings of normal, decreased and increased photoreceptor layer thickness in areas next to drusen suggest that the structure-function relationship could be more complex than previously considered.

African-American patients with AMD

We determined in detail the disease expression of AMD in African-American (AA) patients and compared the results to those of Amish AMD patients. Following on our quantitative observations in intermediate non-neovascular AMD in the Amish, we studied the AA AMD

patients with spectral-domain OCT (and autofluorescence imaging in a subset). Macular location and characteristics of large drusen (≥125 µm) were determined. Thickness of photoreceptor laminae was measured overlying drusen and in other macular regions.

Qualitative observations that preceded our quantitative studies revealed a spectrum of severity of disease in our AA patient cohort and these observations were comparable to earlier published studies. Drusen were associated with normal autofluorescence, or locally increased or decreased autofluorescence. Cross sectional images by OCT showed drusen as elevations of the RPE layer. Some eyes showed numerous small patches of increased and decreased autofluorescence and subretinal drusenoid deposits which contrasted to the sub-RPE location of typical drusen. There was also (in some AA-AMD patients) amorphous-appearing hyperreflective material beneath the foveal region with apparently thinned foveal and surrounding ONL. Images representative of advanced AMD with central geographic atrophy were present in one patient. The atrophic areas had markedly reduced autofluorescence. OCT showed increased choroidal reflectivity and disruption of normal retinal laminar architecture with loss of ONL in the atrophic region. Another notable OCT feature in the advanced AMD eye was thickened subretinal material across the central retina.

The spatial distribution of the large drusen that we analyzed in the AA-AMD eyes (n=183) was determined. The majority of these drusen (117/183; 64%) were concentrated in the pericentral zone (the outer circle extending from 1.5 to 3 mm eccentricity). The central zone (foveal circle and surrounding annulus to 1.5 mm eccentricity) showed a lesser drusen concentration (52/183; 28%). This is in contrast to the results from our Amish intermediate AMD cohort analyzed with the same methods; the Amish patients (n=104) showed a large drusen concentration in the central zone of ~60% while the pericentral zone was 36%. The proportion of drusen classified as central was highly significantly different between the two cohorts (p=0.004, GEE logistic link; reference 2 in item 20 of this report); including age in the model (p=0.829) did not substantially alter the statistical significance of the difference between cohorts (p=0.005, GEE logistic link). Also different in these two groups of patients classified as intermediate AMD were the widths of drusen. In AA-AMD eyes, drusen width was 263±94 (mean±SD) µm, which was smaller than the average width of drusen (352 ±153 µm) in our Amish AMD cohort. This difference was highly statistically significant (p=0.001) even after adjusting for age (p=0.005; GEE identity link). Differences in drusen distribution and drusen width between the two racial groups were not due to differences in drusen load. The average number of drusen per eye (eyes averaged if OD and OS both had drusen) was 9.7 (SD=8.6) in the AA cohort and 11.7 (8.6) in the Amish cohort which was not significantly different (p=0.32, two sample t-test). This difference was even less significant (p=0.73, analysis of covariance) when adjusted for age.

We quantified the photoreceptor layers in the AA-AMD eyes with large drusen (≥125 µm) and no advanced disease features (n=17 eyes) and compared the results to those of a group of older normal AA subjects without AMD (n=13 eyes). There were significant abnormalities in the photoreceptor laminae overlying the large drusen. When the ONL thickness measured at the peak height of each druse was compared to location-matched control values, there was significant (>2SD) thinning at 170/183 loci (93%) loci. The average reduction in overlying ONL thickness was 41% of the mean normal value. The degree of ONL thickness reduction was strongly related to maximum drusen height (r^2=0.49, p<0.001, 53% decrease in ONL per 100 µm increase in drusen height, GEE identity link). These reductions in ONL overlying drusen were accompanied by changes in the photoreceptor IS+OS layer. The reduction in IS+OS layer

thickness was also strongly related to drusen height (r^2=0.34, p<0.001, 45% decrease in IS+OS per 100 µm increase in drusen height, GEE identity link). There was correlation (r^2=0.37) between the thickness fractions of ONL and IS+OS overlying drusen. This correlation between thickness fractions was highly statistically significant (p<0.001, GEE identity link). These results were similar to those we found in the Amish group of patients with large drusen.

Prompted by our recent finding of regions with increased ONL thickness in Amish with intermediate AMD (reference 1 and above), we asked whether AA-AMD eyes also had thickened ONL in areas near or distant to drusen. ONL thickness was measured in the macula in areas neighboring drusen (described as 'paradrusen') with normal-appearing retinal lamination without RPE elevation and as close as possible to previously-identified drusen. These paradrusen measurements were performed similar to the analyses over drusen. The majority of paradrusen loci (158/182; 87%) showed ONL that was within normal limits. At a minority of loci, ONL was significantly reduced (6/182; 3%). We also found significant ONL thickening in some paradrusen regions (18/182 locations; 10%). Paradrusen locations with thickened, thinned or normal ONL were found at all eccentricities measured.

We tested the hypothesis that, like intermediate AMD in Amish eyes, there were regions of thickened ONL apart from the paradrusen locations we detected. High resolution maps of ONL topography were generated in a subset of patients. A 77-year-old female patient had 24 large drusen; some were in the pericentral region and others more centrally located, with the majority associated with overlying ONL thinning. The difference map confirmed the presence of several paradrusen loci with thickened ONL. A region of ONL thickening was also detected in the central zone, at least 400 µm from the closest drusen. A 60-year-old female patient had 13 large drusen and these were located both in the pericentral and central zones. Patchy ONL thinning was found and related to the sites of the drusen. There were only limited sites of paradrusen ONL thickening detectable in this patient. A 68-year-old male patient had only 4 large drusen and these were associated with ONL thinning. There were some paradrusen areas with ONL thickening but more extensive retinal regions (mainly in the superior macula) distant from drusen that showed thickened ONL.

We confirmed in this study that there is a pericentral distribution of drusen across AA-AMD maculae; this is in contrast to the central localization in our Amish AMD cohort. Reductions in the photoreceptor laminae overlying drusen were evident. ONL thickening in some macular areas of AA-AMD eyes was detected and, as we hypothesized for Amish AMD, these may be an early phenotypic marker for photoreceptor stress.

Phenotyping by contrast sensitivity: Contrast sensitivity is a measure of the threshold contrast for seeing a target and has been reported to be impaired in both early and late AMD. Our goal was to measure contrast sensitivity for small targets presented at the locations of identified drusen and compare these with measurements made at healthy eccentricity-matched areas of retina.

METHODS

On each trial of the experiment the subject fixated a small central spot against an otherwise uniform achromatic background. Stimuli were presented using a carefully-calibrated (PhotoResearch PR-650 spectroradiometer) computer-controlled monitor (ViewSonic 22"

G220fb) with high precision intensity resolution (14-bit Bits++, Cambridge Research Systems). An infrared video eye tracker (SR Research, EyeLink 1000) monitored fixation and trials were initiated when the eye tracker indicated that subjects were fixating. In cases where the eye-tracker could not reliably lock onto the subject's eye position, this step was omitted. Small (~0.3 degree) Gaussian blob targets were presented using a random time schedule and subjects indicated via a button push when they detected a target. Target positions were determined using Fundus photos acquired for each subject, Calibration psychophysical detection data were obtained for each subject to localize his or her blind spot. These data was then used to register locations on the computer screen to locations on their fundus photos, by aligning the psychophysically-characterized blind spot with the optic disk in the fundus photo. For experimental subjects (patients), the size and location of the Gaussian targets was tailored to the size and location of drusen identified in fundus photos. For both experimental and control subjects, targets were also placed over blood vessels and over regions of healthy retina. Experimental subjects were patients selected from both AA and Amish populations. Control subjects without history of eye disease, primarily UPenn undergraduates, were also studied for the purpose of developing and validating the experimental procedures.

RESULTS

In total, we studied 39 subjects, of which 22 subjects were excluded due to inability to fixate during the experiment or inability to observe the stimulus, even at high contrast. Of the 17 valid subjects, 9 were control subjects and 8 were experimental subjects (patients). Across these 17 subjects, we successfully measured sensitivity data for 41 target regions. For each of these, targets were presented at a closely spaced series of iso-eccentric positions on the retina that, based on the subject's fundus photograph, crossed either a blood vessel (17 targets), a druse (8 targets), or neither (16 targets). Measurements for each region thus consisted of a sensitivity-vs-position curve, where the positions were finely spaced across the specific location of interest and sensitivity was taken as percent of presented targets successfully detected. In order to determine if we were able to accurately measure the contrast sensitivity at our target locations, we first asked if we observed a dip in sensitivity-vs-position for those targets located over a retinal blood vessel, as compared to those targets that overlapped with neither a blood vessel nor a druse. We tried a number of automated approaches to this problem, none of which were satisfactory. As an alternative, which we found effective, we asked three human raters to categorize each sensitivity-vs-position curve, presented masked as to subject and target position, as either containing or not containing a dip in sensitivity. All three raters agreed on their ratings of 10 of 16 control positions and 10 of 17 blood vessel positions. For control subjects, both sensitivity and specificity for all three raters were between 60 and 90%, indicating an above-chance classification accuracy and suggesting that localized contrast sensitivity measurements in control subjects was possible in the experiment. For experimental subjects, however, sensitivity and specificity were not above chance and thus our measurements were not able to reliably indicate contrast sensitivity at the precision required to determine whether such sensitivity is reduced over the location of drusen. We believe, the reason for the difference between control and experimental subjects is related to their ability to fixate reliably. Indeed, the performance of the eye tracker for the experimental subjects was not as reliable as for control subjects. This in turn may be related to age, as the control subjects were in general younger than the experimental subjects.

In addition to finalizing our analyses of the contrast sensitivity experiment, we also finalized and published a paper on an unsupervised learning method for determining the classes (long-, medium-, or short-wavelength-sensitive) and positions of the cones in the photoreceptor mosaic of the retina. This project grew out of an effort to understand how changes in the sensitivity of patches of retina, e.g. by the presence of drusen in macular degeneration patients, might affect the visual system's representation of the photoreceptor mosaic. In our paper, we found that our unsupervised learning technique was capable of learning both the classes and positions of the retinal cones from visual experience alone. This paper was published in *PLOS Computational Biology*.

Aim #3. Brain structure and function in response to changes in visual experience

The objective of this aim was to determine where, in a subgroup of AMD patients with central visual loss that transition to using a peripheral patch of retina as a new fovea, there is also a shift the cortical visual representation. The goal was to assess the presence of cortical plasticity with functional magnetic resonance imaging (fMRI) in AMD subjects with bilateral central visual loss. The target for this study was 30 cases and 10 controls.

METHODS

Suitable subjects were selected from the U. of Penn. Clinical Practices in the Dept. of Ophthalmology. During fMRI scanning, subjects viewed a screen that subtends 22° of visual angle. The screen is divided into 60 sections defined by concentric rings and radii. Each section is activated with a multi-focal stimulation protocol. Fixation was always with respect to the macula, and not with any PRL. Eye position was monitored during scanning using an infrared eye-tracker (Applied Science Laboratories LRO-6). Scanning was performed in 7 minute blocks of Blood Oxygen Level Dependent (BOLD) fMRI (3mm isotropic, whole-brain volumes at a TR of 3 seconds) over the course of 90 minutes, including breaks and the acquisition of a high-resolution (1 mm) anatomical, MPRAGE image. The anatomical image from each subject was analyzed using the FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) toolbox. The raw data were then compared to a standardized template of retinotopy that we developed as part of this project.

RESULTS

We conducted 28 control subject MRI scanning sessions with both visual retinotopic mapping and with resting-state fMRI data (brain activity measured from awake subjects in darkness). These retinotopic mapping data were used to create a predictive map of primary visual cortex organization based upon anatomy alone. We further refined and extended this anatomical template in a replication data set, confirming our ability to specify retinotopic organization with a precision of approximately 1° of eccentricity (within the central 20° of vision) and approximately 15° of polar angle. This template approach allows us to predict the cortical location of the "lesion projection zone" for patients with homonymous vision loss, and test for alterations in cortical organization at that site. We then extended this anatomical prediction approach to extra-striate visual areas, and showed that similar prediction of retinotopic organization may be achieved for visual areas V2, V3, and hV4. Developing the template was

crucial for allowing us to understand whether retinotopy in patients differed significantly from what it would have been before the onset of central vision loss.

We were able to study four patients with advanced AMD who were identified by our collaborators in the other aims of this project. Of those four, two had the required combination of demarcated, homonymous central scotomas and the ability to participate with the scanning study. We have studied these two patients on each of two occasions. Analyses of these data—combining our ability to target cortical regions with an anatomical template and assess functional connectivity with resting-state data—suggest altered cortical functional connectivity between the lesion projection zone in the occipital pole and the cortical region sub-serving a preferred retinal locus.

Unfortunately, we were not able to continue recruiting AMD patients with the required combination of demarcated, homonymous central scotomas. Our problem in identifying these subjects is most likely related to the environment of the Penn Ophthalmology practice and the paucity of central scotoma patients seen at this location. Due to recruitment problems, this aim will go unfinished. Still, we were able to make the most use of our normal patients and have shown that cortical anatomy may accurately predict the retinotopic organization of primary visual cortex (2 manuscripts published). In addition, we measured spontaneous cortical neural activity from the human visual cortex in complete darkness and found subtle but systematic alterations in patients with blindness (1 manuscript published, one submitted).

Aim #4A-C. Pilot Study to Identify Barriers for Routine Eye Care

The objective under this Aim was to create and pilot test a questionnaire that sought to measure the reasons people did not seek out health care. In order to meet this objective, the Lincoln University (LU) team completed a literature review, developed a questionnaire designed to elicit barriers to eye care (Visual Health and Access to Eye Care), consulted with study focus group members (students, parents, eye-care physicians) who reviewed the questionnaire for its ability to answer questions it is designed to answer (face validity), secured LU Institutional Review Board (IRB) approval, and trained student assistants.

This pilot study of the developed questionnaire was designed to ferret out bugs in the questionnaire design and its actual implementation, to make sure that the questionnaire is efficient in that the least number of questions is used to asses the needed information, and to assess its ability to provide similar results when repeated in a second sample of the same cohort (reliability). The questionnaire was administered to targeted minority groups during two major campus events where significant numbers of parents and relatives of students were present (approximately 100 participated in November 2010 and approximately 76 participated in March 2011). The two samples had minimal overlap of participants. Since the surveys were anonymous, the few overlapping subjects could not be removed in analysis.

METHODS

The questionnaire was designed with four categories of questions that, based on prior evidence were thought to be associated with one of four different impediments (or enablers) related to obtaining eye care. The intent of each of the questions can be categorized into four groups as given in Table 1.

Table 1. Questions related to each of the major categories

Impediments or Enablers	**Questions related to Category**
Visit (factors that relate to trust and communication that one may have during a visit to their doctor)	17. Communication with Doctor 18. Resources for Learning about Eye Care 19. Trust in Doctor 20. Last routine check-up
Exam (denotes the results of an examination performed by an eye doctor)	4. Last time eyes were examined 6. Last time eyes examined with dilated pupils? 7. Ever told by eye Dr. you need glasses? 9. Ever told by eye Dr. or *HCP you have AMD? 10. Ever told by eye Dr. or HCP you have diabetes? 11. Ever told by eye Dr. or HCP you have diabetes damage to eyes? 12. Ever told by eye Dr. or HCP you have glaucoma?
Access (represents the extent to which elements such as transportation, cost, health care insurance, might interfere with going to visit the doctor)	5. Reason you have not visited eye Dr. in 12 mos. 13. Do you have health care insurance? 14. Do you have primary care Dr.? 15. Not visited Dr. in past year because of cost? 16. Not visited Dr. in past year because of transportation?
Health (refers to both general health and eye health)	1. How is general health? 2. Difficulty seeing across street? 3. Difficulty reading documents? **8.Ever told by eye Dr. or HCP you have cataracts?

* (HCP – Health Care Provider)
**We theorize that Question 8 falls into the category of "Health" because African Americans may be more knowledgeable about cataracts (more so than other eye ailments) and thus associate it with general health

RESULTS

Assessment of the actual implementation of the questionnaire design.

LU students were recruited and selected to participate as interviewers. The LU team understood and considered the importance of training interviewers to be competent, professional and sociable. To that end, several students were asked by LU team members to consider becoming part of the research project. Qualities such as experience, classification, grade point average, and reliability were strongly considered in the selection process. Once identified, a core group of approximately 6-8 students participated in training sessions, conducted by LU team members, that focused on orientation about the project as well as research and interviewing processes. Students were coached and practice sessions of simulated interviews were conducted.

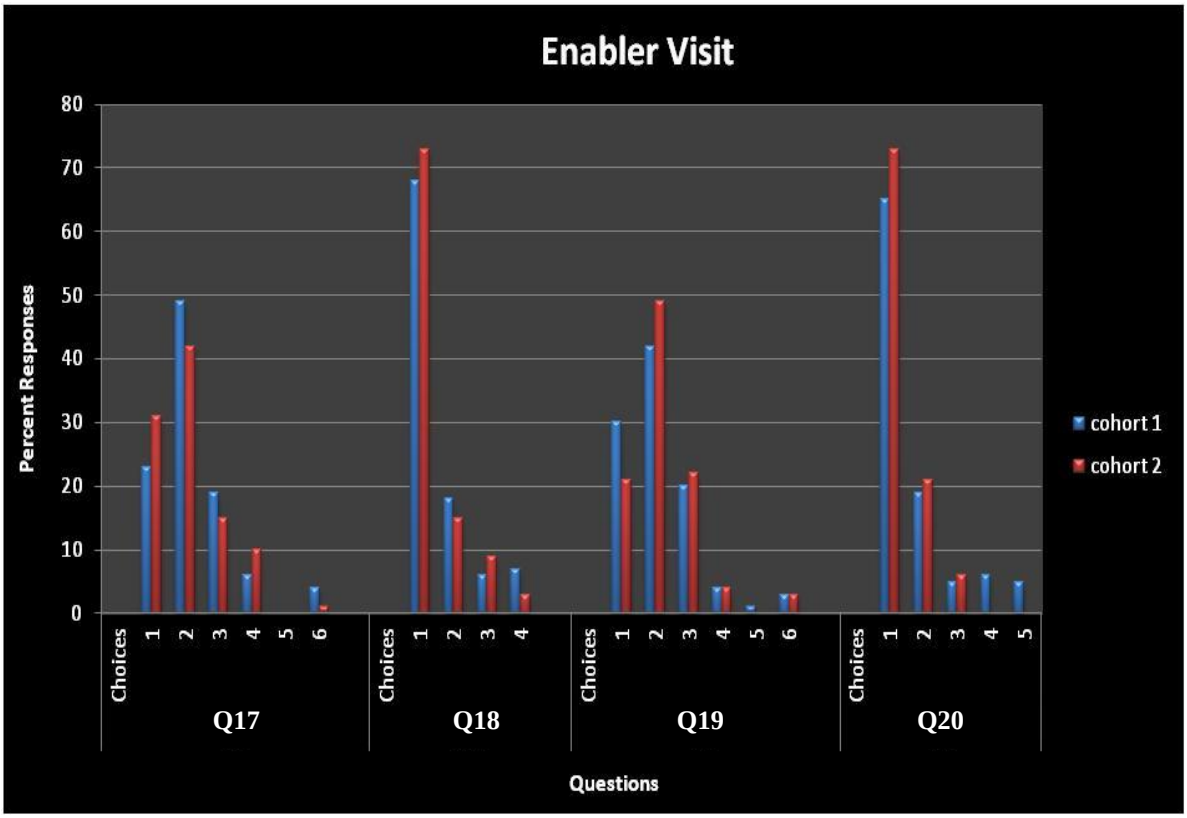
On the two respective days of the actual interviews 3-4 students were situated near the front door of the venue. Tables were set up with pencils, and forms including release of information,

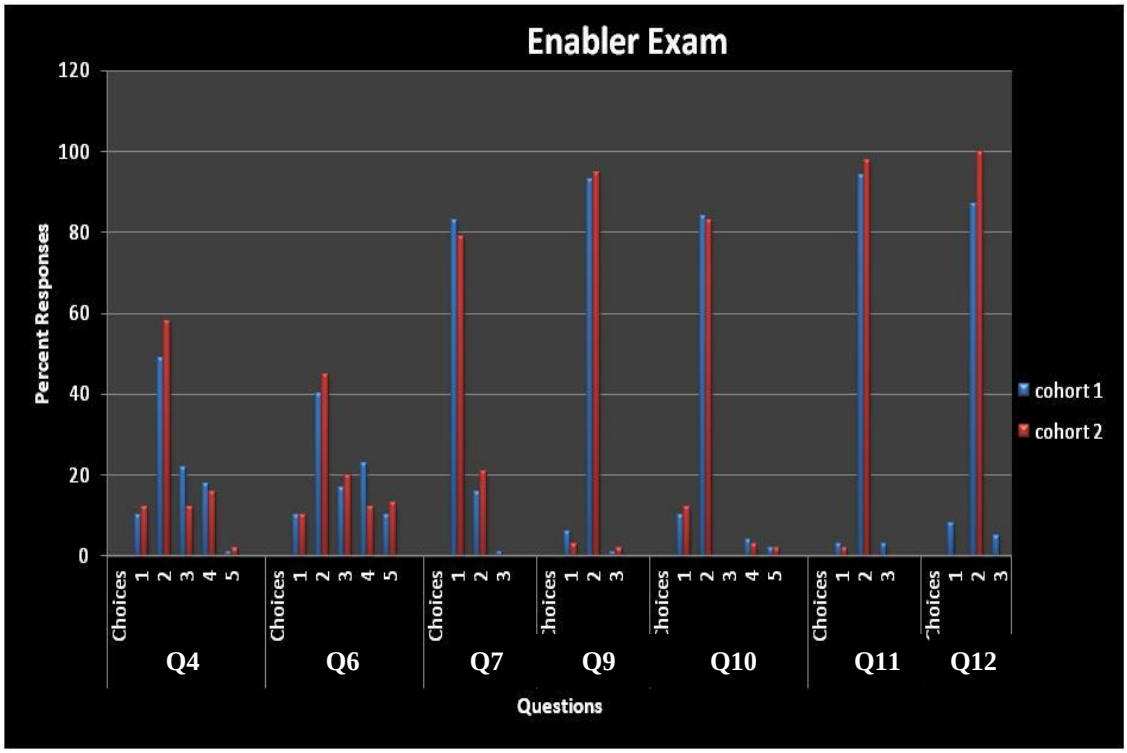
confidentiality, and survey questionnaires. Students greeted incoming parents, relatives, and friends of honorees and invited them to complete the 20 item study questionnaires that took approximately 10 minutes to complete. LU team members supervised the activities but, for the most part, allowed students to lead and facilitate the initiation and collection of questionnaires. Most respondents appeared to be willing participants. Some posed study-related questions to the students and LU team members. For the most part respondent's reactions seemed to be supportive since congratulatory and encouraging remarks were offered about student involvement in the research project. Also, it was observed that some would continue conversations about eye care related concerns after their surveys were submitted to the collection box. Thus, it is reasonable to conclude that the overall experience on the part of respondents seemed positive while the students gained important research experiences.

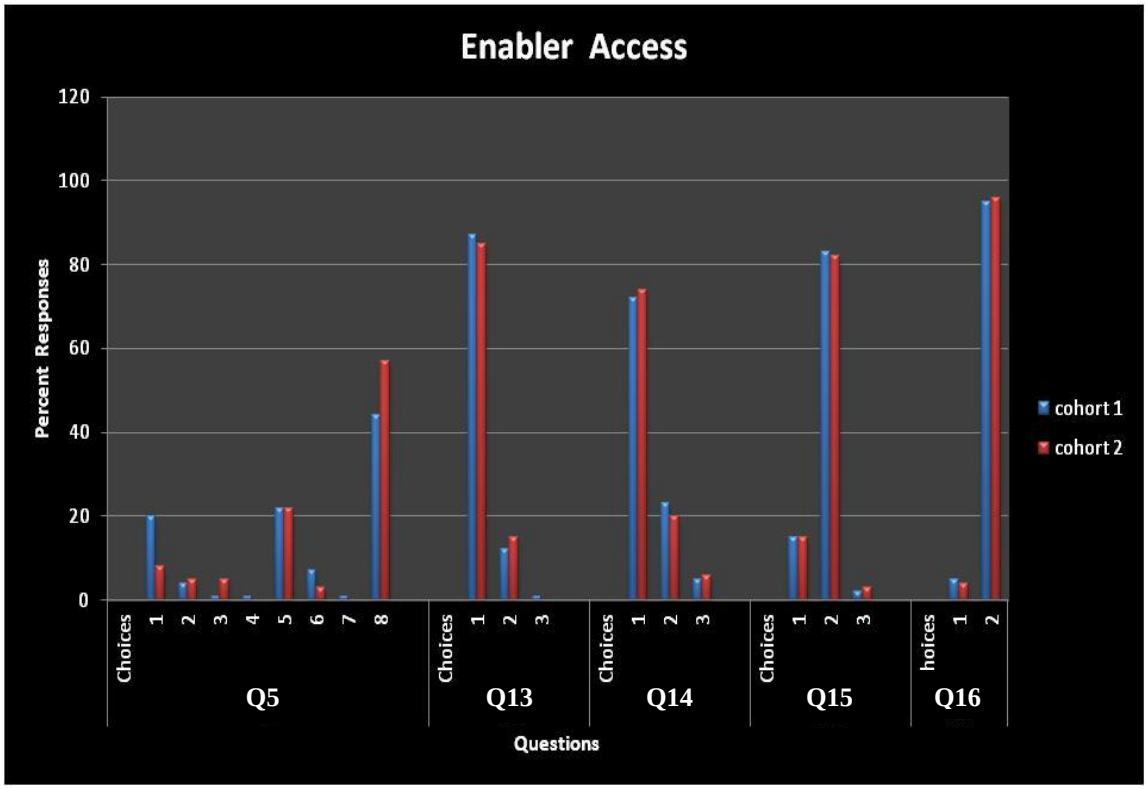
Assessment of the ability of the questionnaire to provide similar results when repeated in a second sample of the same cohort (reliability).

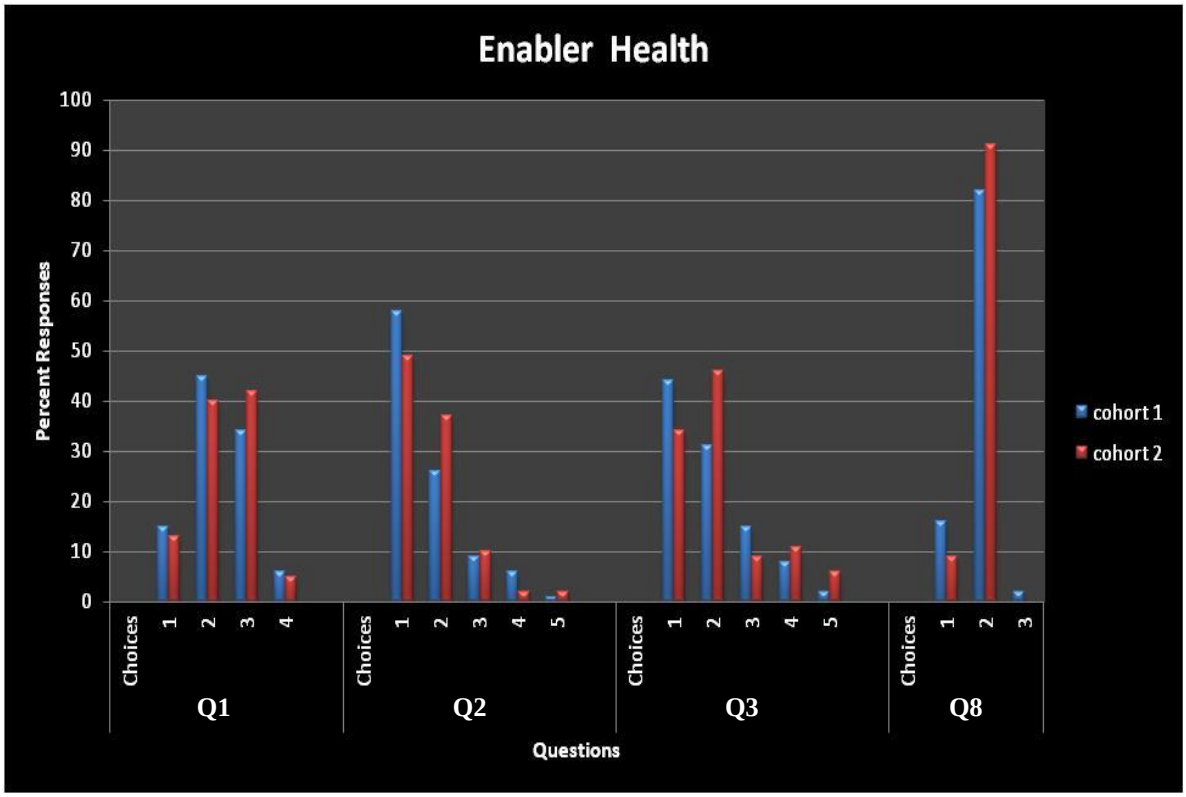
The LU team was concerned that the willingness to agree to the interview would be impeded considerably if potential respondents were informed that they would be contacted again for a second interview. The issues raised would have been those of confidentiality and not wanting to commit to a second survey. For that reason, we decided to promise complete anonymity, and not to test and then track the individual test takers. The survey gave very similar results with the different samples from the Lincoln University population and therefore it is reasonable to conclude that the results are reproducible upon repeated sampling from the same AA population. While having a second sample and finding similar answers could mean that the survey actually will give a different answer on a different sample but that the sample differences in this case cancelled out the survey instrument differences, this is considerably less likely than the conclusion that the samples are from the same population and so the survey gives similar results. This is a form of reliability but not necessarily following the classical definition.

The frequency distribution of responses to each of the 20 questions was compared between the two cohorts. The results are shown in the Figures below for each of the categories in Table 1. With the exception of Q 12, there were no statistically different response distributions for the dichotomous and polychotomous questions in the two cohorts, for each of the 20 questions. In the responses to Q 12, the proportion of subjects reporting having been told they had glaucoma was 8.3% in the first interview and there were no such reports for those in the second interview


Enabler Visit
Percent Responses
80
70
60
50
40
30
20
10
0
Choices
1
2
3
4
5
6
Q17
Choices
1
2
3
4
Q18
Choices
1
2
3
4
5
6
Q19
Choices
1
2
3
4
5
Q20
Questions
cohort 1
cohort 2


Enabler Exam
Percent Responses
120
100
80
60
40
20
0
cohort 1
cohort 2
Choices
Q4
Q6
Q7
Q9
Q10
Q11
Q12
Questions


Enabler Access
Percent Responses
120
100
80
60
40
20
0
cohort 1
cohort 2
Choices
Q5
Q13
Q14
Q15
Q16
Questions



Assessment of the hypothesized groupings of the questions on impediments and enablers. The PCA results were not completely similar in the two cohorts, and neither exactly reflects the results in the total cohort seen in Table 1. The four categories included the questions indicated in Table 2 below for each of the two cohorts.

COHORT I RESULTS ALONE	COHORT II RESULTS ALONE
Visit = Q17, Q18, Q19, Q20 **Exam** =Q4, Q5, Q6, Q7 **Access** =Q9, Q10, Q11, Q12, Q13, Q14, Q15, Q16 **Health** =Q1, Q2, Q3, Q7, Q8	**Visit** =Q17, Q18, Q19, Q20 **Exam** =Q4, Q5, Q6, Q7, Q15, Q16 **Access** =Q9, Q10, Q17, Q18, Q19 **Health** =Q1, Q2, Q3, Q8, Q13, Q14, Q15

In both cohorts, the first factor perfectly reflects the questions originally designed for the category VISIT (questions 17-20) and is the only factor that can be easily separated from the other principal component factors. The fourth factor in both cohorts includes questions 1,2,3,8 in the original category HEALTH, but is mixed with other questions including question 7 (whether

an eye Doctor has informed the individual to wear glasses) and questions 13-15 from ACCESS. The other two factors seem to be the mixture of questions in categories ACCESS and EXAM because those questions are more correlated. The factor analysis method is based on the correlation matrix of the variables involved and correlations usually need a large sample size before they stabilize. The first cohort included 109 participants and the second only included 67. Both are considered to be a small sample size for factor analysis and thus these results may not be reliable; while combined, the total number 176 is close to a fair sample size and may exhibit more reliable results (Tabachnick and Fidell, 2001). To have a more reliable comparison, the sample size needs to be increased to at least 200 in each cohort. Based on what we have so far, the results seem promising in separating some categories. Tabachnick, B. G., & Fidell, L. S. (2001). *Using multivariate statistics* (4th ed.). Needham Heights, MA: Allyn & Bacon.

Assessment of the efficiency of the questionnaire design.

SAS PROC FACTOR for Principal Components Analysis (PCA) was used, an approach for data reduction used very heavily in the behavioral sciences. The PCA results ended in the creation of the four groups of factors (based on the 20 questions on the questionnaire) seen in Table 1. In its simplest terms, these groups of questions are similar within each group and to different degrees dissimilar to the questions in different groups. The results indicate that the questions in the original categories proposed by the questionnaire team were reasonably well targeted and are serving their intended purpose. The full set of 20 original questions remained intact albeit for analytic purposes they were reduced to 4 functions of mutually exclusive sets of the 20 questions. Looking at only paired correlations of the 20 questions (190 correlations), there were 30-40 statistically different correlations using the nominal alpha level of 0.05.If these were independent questions, we should expect about 190 X .05≈10 significant results (under a null hypothesis of no correlation). Thus there is certain correlation structure in the data, with higher correlations of questions within each category than correlations between questions from different categories.

- These correlations appeared both within the four categories and between the four categories. With the small sample size in this pilot study, we believe that assessment in a larger cohort should be done to tease out higher level correlations and to make sure the reductions to the four factors indeed does not contain redundant questions.
- These results were based on specific assumptions used in the PCA, for example each variable should be continuous; here we only have pseudo-continuous variables (all answers to the questions are categorical)that if modified could have changed the results, perhaps eliminating one of the four component, or modifying the question placements within the groups.

FOLLOW-UP BASED ON THE COMMENTS AND RECOMMENDATIONS OFFERED BY THE PA-DOH INTERIM PERFORMANCE REVIEW

Following the directives and recommendations offered by the PA-DOH Interim Performance Review team in late November 2011, the LU team worked to make related report modifications. Highlights included further statistical examination and justification for use of the Principal Component Analysis (PCA) method to analyze collected data, revising the study questionnaire,

and clarifying as well as completing the final report related to Aim # 4- *Identifying Barriers for Routine Eye Care.*

The LU team also updated its survey to address the comments/recommendations made by the state reviewers. There was refinement of the instrument to make questions specific to vision care. Another psychosocial question (#18), pertaining to religion was added. Also, there was an inclusion of indicators of literacy and numeracy skills question (#'s 22 and 23) (Permission to use questions 22. and 23. granted via Correspondence: Paul P. Lee, MD, JD, Box 3802, Duke University Medical Center, Durham, NC 27710 (lee00106 @mc.duke.edu).

Finally, though there are many research limitations, as is often common in a pilot study, the LU team believes that they have developed a modified valid and reliable approach to assessing and surveying a general African American population. This contention is backed by the approach and population used to pilot the survey. A population of individuals that attended two respective Lincoln University (LU) "Convocation" events (November 2010 and March 2011) completed the Visual Health and Access to Eye Care Questionnaire. For the most part, the groups were made up of relatives of LU undergraduate students including parents, guardians, grandparents, and extended family/community members. The undergraduate population of LU is approximately 1,800 students, 90% of whom are "Black". The 2010 LU Fact Book (Lincoln University - Office of Institutional Research, "Lincoln University Fact Book: 2010") notes that 50% of the students are Pennsylvania residents. Fifty-six (56%) of those from Pennsylvania are residents of Philadelphia. A significant proportion, approximately 90 % of these students qualify for government/state financial assistance. Regarding income data 22 % of student households are over $60,000, 28 % have a range of - $30-60,000, and for 50 % income is less than $30,000. Considering this profile, it is reasonable that the Visual Health and Access to Eye Care Questionnaire may be a useful instrument if administered in urban areas surrounding LU, particularly Philadelphia, PA. It is recommended that further interviews and sampling be utilized in and by Eye care and related healthcare facilities. Associated practitioners may also find that use of questionnaires on sampled respondents from African American churches, community centers and the like can provide useful information that will ultimately help to develop enhanced strategies of prevention, treatment, and better eye health outcomes.

Aim #4D. Student Internships

The goal of this project was to provide (1) student internships to four minority graduate students recruited from the University of Pennsylvania or Temple University or Lincoln University and (2) student internships to four minority undergraduate students recruited from Lincoln University.

Funds from this grant were used to pay stipends for 1 graduate student, 3 undergrad students and 5 post-doc fellows.

Abstracts

1) The Vision Rehabilitation in African Americans with Central Vision Impairment Study: Design, Methodology and Preliminary Result. *Spring Vision Conference, PennDel Association for the Education and Rehabilitation of the Blind and Visually Impaired 2012.*

2) Restoring Hope through Vision Rehabilitation: Improving Services to Older African Americans. National Association of Social Workers National Conference *Restoring Hope: The Power of Social Work* 2012.

3) Vision Rehabilitation for African Americans with Central Vision Impairment (VISRAC) Erin M. Draper, OD,FAAO; Rui Feng, PhD; Sarah Appel, OD, FAAO; Marcy Graboyes, MSW, ACSW, LSW; Erin Engle, BS; Elise Ciner, OD, FAAO; Jonas H. Ellenberg, Ph.D.; Dwight Stambolian M.D. , Ph.D. *Accepted for presentation at the American Academy of Optometry Annual Meeting, Denver, CO 11/14.*

4) Benson NC, Brainard DH, Stambolian D (2012) Contrast sensitivity at soft drusen in early age-related macular degeneration using fine-detail perimetry. Poster presented at the 2012 Annual Association for Research in Vision and Ophthalmology (ARVO) Meeting. 4-10 May.

5) Benson, N. C. & Brainard, D. H. (2012). An Unsupervised Learning Technique for Typing Cones in the Retinal Mosaic. VSS Annual Meeting, Naples, FL, 2012. http://www.journalofvision.org/content/12/9/1167, doi: 10.1167/12.9.1167.

6) Benson, N. C., Butt, O. H, Datta, R., Brainard, D. H. & Aguirre G. K. (2011). A universal retinotopic mapping of V1 with respect to anatomy. VSS Annual Meeting, Naples, FL, May 6-11, 2011. http://journalofvision.org/11/11/1067, doi: 10.1167/11.11.1067.

7) Butt, O. H., Benson, N. C., Datta, R., Brainard, D. H. & Aguirre G. K. (2011). Multi-focal and phase-encoded retinotopy compared. VSS Annual Meeting, Naples, FL, May 6-11, 2011. http://journalofvision.org/11/11/1069, doi: 10.1167/11.11.1069.

8) Benson, N. C., Butt, O. H, Jain, S., Brainard, D. H. & Aguirre G. K. (2013). Cortical surface structure predicts extrastriate retinotopic function, VSS Annual Meeting, Naples, FL, 2013. http://journalofvision.org/13/9/271, doi:10.1167/13.9.271.

9) Butt, O. H., Benson, N. C., Datta, R., and Aguirre, G. K. (2013). Blindness subtly alters the distant functional connectivity of dorsal and verntal extra-striate cortex. VSS Annual Meeting, Naples, FL, 2013. http://www.journalofvision.org/content/13/9/280, doi: 10.1167/13.9.280.

10) Benson, N. C., Butt, O. H., & Aguirre, G. K. (2014) Spontaneous visual cortex activity predicts eccentricity and is related to receptive field size. VSS Annual Meeting, St. Petersburg, FL. http://www.journalofvision.org/content/14/10/587, doi: 10.1167/14.10.587.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

___X___Yes
_____No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

____X_Yes
_____No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

__14__Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

___X__Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
__455_Males
__554_Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_949__Blacks or African American

_____Native Hawaiian or Other Pacific Islander
_60 White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

United States

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
____X_No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
___X___No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated

Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Abnormal thickening as well as thinning of the photoreceptor layer in intermediate age-related macular degeneration	Sadigh S, Cideciyan AV, Sumaroka A, Huang WC, Luo X, Swider M, Steinberg JD, Stambolian D, Jacobson SG	Invest Ophthalmol Vis Sci	2013 Mar 5	☐Submitted ☐Accepted X Published
2. Drusen and photoreceptor abnormalities in African-Americans with intermediate non-neovascular age-related macular degeneration	Sadigh S, Luo X, Cideciyan AV, Sumaroka A, Boxley SL, Hall LM, Sheplock R, Feuer WJ, Stambolian DS, Jacobson SG	Curr Eye Res	2014 Jun 9	☐Submitted ☐Accepted X Published
3. Unsupervised Learning of Cone Spectral Classes from Natural Images	Benson NC, Manning JR, Brainard DH	PLoS Comput Biol	2013 Jan	☐Submitted ☐Accepted X Published
4. The retinotopic organization of striate cortex is well predicted by surface topology	Benson, N. C. Butt, O. H., R. Datta, P. D. Radoeva, D. H. Brainard, G. K. Aguirre	Current Biology	2012 June	☐Submitted ☐Accepted X Published
5. Correction of distortion in flattened representations of the cortical surface allows prediction of v1-v3 functional organization from anatomy	Benson, N. C. Butt, O. H., Brainard D. H., & Aguirre G. K.	PLoS Computational Biology	2013 July	☐Submitted ☐Accepted X Published

6. The fine-scale functional correlation of striate cortex in sighted and blind people	Butt OH, Benson NC, Datta R, Aguirre GK	Journal Neuroscience	Jan. 2013	☐Submitted ☐Accepted X Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes___X_____ No_____

If yes, please describe your plans:

Article on clinical trial.
Article on genotyping results.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

NONE

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

NONE

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No___X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

No new key investigators added to the project beyond the original proposed.