REPORT OF THE OCULAR EPIDEMIOLOGY STRATEGIC PLANNING PANEL

Epidemiological Research: From Populations through Interventions to Translation

September 2007

Overview

The National Eye Institute (NEI) is committed to the goal of protecting and improving visual health. To be accomplished successfully, this goal will require a multi-disciplinary approach that encompasses basic, clinical, and public health sciences. The multi-disciplinary approach is embedded in the current *National Plan for Eye and Vision Research (2004)*, wherein this Panel noted that the disease-specific program plans include epidemiological investigations as priorities. Such an approach is an important integration of epidemiology, which is a methodological science, into eye and vision research. For the purposes of this report, the term epidemiology will be used in the broad context, which includes classic observational studies, clinical trials (particularly randomized clinical trials), statistical genetics, and health services research.

Use of classic epidemiologic techniques in diverse groups of people has advanced our understanding of infectious, environmental, behavioral, and sociocultural factors that underlie disease incidence, progression, and outcome, and has produced the evidence for effective prevention and treatment strategies. Although the tools of epidemiology were developed to investigate the causes and cures for epidemics of infectious disease, modern epidemiology has applied these successfully to investigations of chronic diseases, which now represent the majority of burden of illness in the United States and in most developed countries. In the best sense of a multi-disciplinary approach, epidemiology is one component in the continuum of "bench to person to population" studies necessary to fully understand the pathogenesis of disease, the impact in populations, and the results of interventions. Ideally, rather than a linear continuum, this is a creative feedback loop in which the results from epidemiological investigations return to laboratory scientists who produce new insights at the genetic, molecular or cellular levels that can be tested in human population studies in conjunction with other exposures. At the other end, epidemiological findings are also at the interface with health services and social science researchers who provide insights into improved strategies for public health interventions. Indeed, a firm understanding of the behavior of disease in human populations is fundamental to the development and delivery of effective interventions. Ophthalmic epidemiology then is part of the core strategy of the NEI for improving visual health, with the broad aim of reducing the burden of visual impairment in populations through research into the causes, diagnosis, prevention, treatment, and rehabilitation of the major blinding diseases.

More recently, epidemiology has been undergoing an evolution, paralleling the remarkable technological advances in molecular medicine, the realization of the powerful ecological forces that affect populations, and the rapid development of interventional tools on the horizon. The ability to apply genetic and molecular biological tools in the context of populations, in connection with behavioral, environmental, and social factors, has broadened considerably the potential contribution of epidemiology to the goal of controlling the major blinding diseases. Such opportunities are an exciting component of the classic armamentarium of observational and clinical trial methodologies in epidemiology. The Panel has been charged with considering these unique opportunities while forging recommendations for future strategic research questions.

The purpose of the Panel's report is to present the broad program goals for ophthalmic epidemiology, to highlight the progress in this field in the last fifteen years, and to recommend research strategies and questions for the next five years.

Program Goals

The broad program goals for ophthalmic epidemiology must support the overall mission of protecting and improving visual health. After careful review of the progress made by epidemiological research, and the opportunities for further contributions, the Panel has developed the following goals, which are not listed in priority order:

- **Determine the burden of eye diseases and their visual outcomes in a changing population, particularly disparities in the burden and the influences of sociocultural and demographic factors.**
- **Determine the genetic, biological, behavioral, and environmental factors that cause ocular disease, and the processes leading to visual impairment resulting from these diseases.**
- **Improve early diagnosis of ocular diseases and their underlying processes through new screening and detection strategies.**
- **Develop and test new interventions that prevent or treat ocular diseases and resulting disability, and identify predictors of response to treatment.**
- **Identify and assess the strategies that will overcome barriers to eye care and convert evidence-based findings into improved patient and population outcomes.**
- **Develop new methodologies to support ophthalmic epidemiological research.**

Highlights of Progress

The contributions from epidemiological research in the past fifteen years since its last evaluation in an NEI strategic plan have advanced our understanding of the magnitude and impact in populations of the burden of blindness and visual impairment and the individual ocular diseases. Epidemiology has contributed significantly to our knowledge of risk factors for the major blinding diseases, and has tested treatment and preventive interventions. Finally, epidemiological research has identified and evaluated health care delivery processes related to the ocular diseases and their consequences. The panel chose to highlight progress within the goals described above, reflecting the major blinding diseases and interventions. A more detailed report of research progress can be found in Appendix A.

Studies of burden and causes of visual loss, disparities in the burden, sociodemographic factors.

- Epidemiological research has provided estimates of the magnitude and causes of visual loss in the US and world-wide, and determined differences between population sub-groups, such as higher rates of different cataract sub-types in African Americans compared to Caucasians, and in women compared to men. African Americans and Latinos have higher prevalence of glaucoma compared to Caucasians, and Asians have more angle closure glaucoma. Although Caucasians and African Americans have similar rates of early age-related macular degeneration (AMD), Caucasians have

higher rates of late AMD. Rates of diabetic retinopathy are high in Latinos. The remarkable rise in rates of myopia, especially among Asians, has been documented and many population studies have shown generational shifts. Research on these differences provides important clues to pathogenic mechanisms that explain such disparities.

- Within the AIDS epidemic, clinical trials have determined the best treatment methods for cytomegalovirus (CMV) retinitis.
- Considerable progress has been made into outcomes of visual loss, including decrements in quality of life, increases in measures of disability, and negative impact on function such as driving, falls, and performance on every day tasks. Such outcomes are key to determining the societal burden of visual loss, and appropriate rehabilitative strategies.

Studies of causes of major blinding diseases and processes leading to visual impairment.

- Epidemiological research has identified modifiable environmental risk factors for major blinding eye diseases. These include smoking for cataract and AMD, ultraviolet B exposure for cataract, and nutritional factors for AMD. Near work has been associated with myopia.
- In addition to aging, research has identified physiological risk factors for diseases, such as intraocular pressure and central corneal thickness for glaucoma, glycemic control and risk of diabetic retinopathy, and markers of inflammation for AMD.
- Family history and high heritability have been shown as factors for AMD, glaucoma, myopia, and cataract. Progress has been made in elucidating the genes associated with eye diseases, for example, complement factor H (CFH) for AMD. Also, the interactions of genes and environment are being identified, such as smoking and variations in HTRA1/LOC387715.
- Use of Polymerase Chain Reaction (PCR) has advanced understanding of infectious disease, and has been used to demonstrate re-emergence patterns of *Chlamydia trachomatis* following mass antibiotic treatment, and to explore the pathogenesis of resistant CMV.
- Case control studies of contact lens associated corneal infections were key to identifying patient and product associated risk factors in these epidemics.

Screening.

- For detecting amblyopia, autorefractor methods had a higher sensitivity than visual acuity screening methods using HOTV letter or Lea symbols, and photoscreener methods and stereoacuity screening tended to perform less well than visual acuity screening.
- The development and reliability testing of digital imaging systems for diabetic retinopathy have shown them to be useful systems that are changing screening programs for this disease.
- Intraocular pressure measurement is not sufficiently sensitive for detecting glaucoma so that its use in screening programs is not recommended.

Interventions.

- Clinical trials on vascular endothelial growth factor (VEGF) inhibition and nutrients for AMD represent major advances in treatment for AMD. Recent trials have shown an improvement in visual acuity with use of novel drugs targeting VEGF inhibition.
- Trials demonstrating the efficacy of laser treatment for diabetic retinopathy and macular edema were a major advance in preserving vision.
- Either atropine or part-time patching are effective treatments for amblyopia. The finding that up to a quarter of older children responded to patching or spectacle treatment suggests that plasticity of the visual system extends through the teenage years.
- A large, simple randomized trial has found that a single dose of azithromycin following surgery for trichiasis reduced recurrence by 30 percent compared to topical tetracycline.
- Clinical trials have validated the value of lowering the intraocular pressure in the management of glaucoma, and treating persons with ocular hypertension.
- Clinical trials of treatments for CMV retinitis in patients with AIDS have set the standards for treatments of this condition.
- Trials of posterior chamber intraocular lenses (IOL) have demonstrated superior visual outcomes compared to anterior chamber IOL or aphakia.
- Trials on treatment of ocular melanoma have shown no difference in survival (mortality) outcomes and little difference in quality-of-life outcomes between enucleation and eye-conserving radiotherapy using I-125 brachytherapy. In the trial of pre-enucleation radiation, there was no survival advantage to radiotherapy.
- The Optic Neuritis Treatment Trial resulted in a standardized treatment approach to optic neuritis, an evaluation for those with optic neuritis, and description of the risk factors for the development of multiple sclerosis.

Translational Research to Eye Health Services.

- The creation of simple tools for estimating cataract surgical coverage and documenting cataract surgery outcomes are helping set targets and reduce the global burden of cataract.
- Economic analyses of the cost benefit of screening and treating diabetic retinopathy has shown the overall cost savings to be accrued by society in saving sight from diabetic eye disease.
- An innovative plan using cost benefit analyses for comprehensive eye care services in Australia, rooted in evidence based practices and public health approaches, has the potential for showing economic value to society.
- A greater understanding of patient and health system barriers to use of care, using qualitative and quantitative techniques.

Overarching Methodologies.

- The development of Generalized Estimating Equations, which allowed the use of both eyes (and other correlated data) in analyses while appropriately adjusting confidence limits, permitted more powerful analyses of epidemiological data.
- Expanded use of Rasch analyses and other psychometric testing improved the development and proper use of questionnaires.

- Development of statistical tools for investigating genotype and phenotype relationships and interactions has been essential for genetic inquiries.

Research Objectives

The Panel has reviewed the progress of research in Ophthalmic Epidemiology, and considered the needs and unique opportunities that are present now and in the future. Some of these have already been identified in the program plans created by the other NEI programs, and for completeness these are listed in Appendix B. Several key elements of the next phase were identified that cut across the specific research objectives: (1) Research in populations will broaden its scope from descriptive studies to those that are more hypothesis driven. This will require innovative uses of populations to address questions; (2) Epidemiologists will foster interdisciplinary collaboration with other specialties as appropriate (e.g. visual psychophysics, cognitive neuroscience, behavioral science, health outcomes, economics, genetics, statistics, etc) to move to the next levels of investigation; (3) The development of biomarkers for early identification of disease, and careful characterization of phenotypes, will become a focus to promote treatment and prevention studies. Research groups will need to agree on descriptors (*i.e.*, measurements) for comparisons of phenotypes across studies; (4) When appropriate, clinical trials must become a broader platform in which to conduct studies on pathogenesis of disease and progression.

The panel has identified several specific research strategies and questions that take advantage of the current needs and unique opportunities to advance the program goals. Each one is listed under the program goal and objective that will be advanced by its undertaking.

1. Determine the burden of eye diseases and their visual outcomes in a changing population, particularly disparities in the burden and the influences of sociocultural and demographic factors.

A. Exploit unique opportunities to address research questions of sociocultural reasons for disparities in eye disease or access to eye care.

Research Needs and Opportunities: Researchers should exploit unique opportunities to address research questions of sociocultural reasons for disparities in eye disease or access to eye care. Sociocultural factors and behavioral factors are likely to influence progression of disease to its visually disabling consequences. These have been poorly characterized, and may explain some of the disparities in vision loss from diabetic retinopathy, cataract, refractive error, and glaucoma. This opportunity is a cross-cutting one, in which the research questions would overlap with program goal five.

Research Strategies and Questions:

- Determine sociocultural factors associated with disparities in diabetic retinopathy, AMD, cataract, glaucoma, and access to care for these conditions.
- Determine the sociocultural and behavioral factors, in addition to other risk factors, that influence progression of disease to vision loss.

B. Conduct basic epidemiological characterization of disease-phenotypic descriptions, progression and outcomes, and risk factors.

Research Needs and Opportunities: Basic epidemiological characterization of disease-phenotypic descriptions, progression and outcomes, and risk factors-are indicated where there is a public health problem and such data are absent and needed to move research in these diseases forward. The panel identified strabismus, ocular complications in AIDS cohorts in the era of HAART, and uveitis as diseases that merit such basic investigations.
Research Strategies and Questions:

- Better define phenotype of different types of uveitis or strabismus.
- Develop standardized reproducible and clinically relevant outcome measures for reporting outcomes and to be used in future clinical trials.
- Determine the rate and risk factors for ocular complications in AIDS patient cohort.

C. Create a framework for evaluating the long-term outcomes of interventions, particularly surgical interventions.

Research Needs and Opportunities: There is an urgent need to create a framework for evaluating the long-term outcomes of interventions, particularly surgical interventions. The panel identified a critical need with regard to refractive surgery. The largest natural experiment in ophthalmology is underway, the creation of a large cohort of young persons undergoing refractive surgery for correction of refractive error, with no data on long-term consequences in later adult life.
Research Strategies and Questions:

- Partner with other organizations (public and private) and create a longitudinal cohort of refractive surgery patients with uniform baseline information and long-term follow-up to ascertain the sequelae of this procedure.

2. Determine the genetic, biological, behavioral, and environmental factors that cause ocular disease, and the processes leading to visual impairment resulting from these diseases.

A. Assess genetic and environmental risk factors and the interacting roles of both, in risk of disease onset and progression.

Research Needs and Opportunities: Accurate assessment of genetic and environmental risk factors, and the interacting roles of both, in risk of disease onset and progression will be crucial for a fuller determination of etiology. This research will need unique cohorts or populations that are cost efficient for the disease under study. Clinical trials or high-risk populations will provide useful platforms for these studies. This need is cross-cutting with goal one, to determine, using gene and environmental factors, the reasons for racial and ethnic diversity.
Research Strategies and Questions: Possible research questions include:

- Develop phenotype-genotype characterizations of AMD, diabetic retinopathy, glaucoma, refractive error, cataract, uveitis, and amblyopia.

- Determine the genetic variations that interact with environmental risk factors that alter onset and progression of diabetic retinopathy, cataract, refractive error and amblyopia, AMD, uveitis, and glaucoma.

B. Characterize physiological risk factors, as well as the genetic and environmental risk factors, to understand onset and progression of relevant diseases.

Research Needs and Opportunities: Better characterization of physiological risk factors, as well as the genetic and environmental risk factors, is needed to understand onset and progression of relevant diseases.

Research Strategies and Questions:

- Identify structural and functional measures for determining early progression of glaucomatous damage.
- Determine the role of vascular factors, e.g., blood pressure or perfusion pressure, in glaucoma.
- Elucidate the ocular structures and visual correlates of abnormal eye growth and development in myopia.
- Determine the physiological content of tears and other systemic ocular factors that influence dry eye.

C. Exploit unique opportunities to obtain ocular samples in the context of therapeutic trials to address seminal questions of pathogenesis and determinants of treatment efficacy.

Research Needs and Opportunities: There are unique opportunities in the context of therapeutic trials to obtain ocular samples including aqueous or vitreous to address seminal questions of pathogenesis and determinants of treatment efficacy (e.g., the opportunity to develop proteomic-genomic biomarkers for predicting early disease onset of AMD, provide risk assessment for progression of disease, and improved molecular imaging of the macula and the retina vasculature). Currently there is a significant opportunity to develop a bank of vitreous samples for patients taken at the time they are undergoing standard of care intraocular injection of anti VEGF therapy. Other examples can include opportunities during trials of any surgical intervention in which aqueous or vitreous can be easily obtained, such as during cataract surgery or surgical interventions for uveitis.

Research Strategies and Questions:

Collect vitreous samples during trials of intraocular injections for AMD before the first treatment instillation, and at each subsequent serial standard of care injection to characterize biomarkers for risk of progression.

3. Improve early diagnosis of ocular diseases and their underlying processes through new screening and detection strategies.

A. Develop and test novel imaging techniques or new biomarkers for disease onset or progression.

Research Needs and Opportunities: In the context of clinical trials or disease cohorts, there is an opportunity to develop and test novel imaging techniques or new biomarkers for disease onset or progression. These are acutely needed for potential trials on prevention of disease onset. The panel recognized these opportunities especially for AMD, diabetic retinopathy, and cataract.

Research Strategies and Questions:

- Develop and test novel imaging techniques, biomarkers, and surrogate outcomes that correlate with disease development or progression.

B. Develop better detection and screening strategies for glaucoma.

Research Needs and Opportunities: The panel recognized a special need to develop better detection and screening strategies for glaucoma where the lifetime rate of blindness or vision loss for those with glaucoma is unknown and may be highly variable. The identification of biomarkers for early identification of those likely to be affected with subsequent vision loss is critical, as it would permit targeted, earlier, and/or more aggressive treatment.

Research Strategies and Questions:

- Determine markers for phenotypes at risk for severe disease and/or rapid disease progression in glaucoma.

4. Develop and test interventions that prevent or treat ocular diseases and resulting disability, and identify predictors of response to treatment.

A. Continue to conduct randomized clinical trials to test preventive or therapeutic interventions.

Research Needs and Opportunities: The panel acknowledges the ongoing need for randomized clinical trials to test preventive or therapeutic interventions, and viewed these as unique opportunities in the following ways. First, the advent of novel treatments such as gene therapy, stem cell interventions, novel drugs and devices and drug delivery systems should be given high priority. Second, the panel recognized that for some diseases there are key issues in trials of timing and/or aggressiveness of treatment needed to delay or prevent progression. Third, trials are platforms upon which risk assessment components (biomarkers and genetics) can be added to identify factors related to treatment efficacy where blood and other ocular samples are obtainable. Fourth, the panel foresees opportunities to incorporate such risk profiles into the design of clinical trials, for example, where patients may be stratified on the basis of biomarkers into alternative treatment arms.

An example of innovative sampling should be applied to trials of the efficacy of VEGF receptor kinase inhibitors in AMD, in which sustained responses are unpredictable and variable. There is a need to develop proteome-genome biomarkers that are useful to assess efficacy of treatment. Therefore, the collection of vitreous or other ocular samples at various time points will add to our knowledge of pathophysiology of disease and treatment response for a number of ocular diseases.

Research Strategies and Questions:
Characterize the genomic markers in vitreous using VEGF trial platforms and determine the complete sequence of the vitreous proteome at three phases of macular degeneration, before during and after successful or unsuccessful therapy with anti-VEGF inhibitors.

B. Determine the genetic variation that can influence and sometimes predict response to treatment.

Research Needs and Opportunities: Underlying genetic variation can influence and sometimes predict response to treatment. Knowledge of such variation can lead to safer and more effective targeted or individualized treatments. The field of pharmacogenetics should be further utilized.
Research Strategies and Questions:

- Characterize the pharmacogenetic interactions in ocular response to drugs.

C. Develop methods to undertake clinical trials in vision rehabilitation.

Research Needs and Opportunities: The panel recognized a special and urgent case for the development of methods to undertake clinical trials in Vision Rehabilitation. Better methods are needed to assess disability due to vision loss and methods that judge the outcome of vision rehabilitation strategies, including rehabilitation potential and coping mechanisms.
Research Strategies and Questions:

- Develop standardized sets of performance base measures, as well as the self reported measures, should be developed to asses the impact of visual impairment, as individuals respond to and cope very differently with visual impairment.
- Develop and rigorously test interventions to decrease disability due to vision loss.

5. Identify and assess the strategies that will overcome barriers to eye care and convert evidence-based findings into improved patient and population outcomes.

A. Develop strategies to enhance patient use of eye care services and to assist providers in more fully implement the results of best-evidence based care practices.

Research Needs and Opportunities: In this broad intersection of epidemiology and health services research, the panel determined two specific areas that complement the previous goals. These are, first, research on strategies to enhance patient use of eye care services, especially overcoming barriers to accessing eye care and improving patient compliance; second, strategies to assist providers in more fully implement the results of best-evidence based care practices.
Research Strategies and Questions:

- Develop and evaluate methods to overcome disparities in access to care and enhance compliance for patients needing care for cataract, diabetic retinopathy, and glaucoma.
- Develop and validate techniques to assist providers to better implement the lessons of best-evidence medicine in their care of patients.

6. Develop new methodologies to support ophthalmic epidemiological research.

A. Develop new analytical, computational, and informatic methodologies to handle high dimensional and/or complex data.

Research Needs and Opportunities: There is an urgent need to develop new analytical, computational, and informatic methodologies to handle high dimensional and/or complex data that is now technologically and financially feasible to collect. Millions of data points can be generated at each of the DNA, RNA, protein, and phenotypic (clinical, ocular imaging, visual fields, OCT, etc.) levels for each study subject. The panel recognizes that developing new methodology is an issue across all NIH Institutes, and every institute should devote resources to advance these developments. These are issues that are not unique to NEI, but the panel recommends that NEI consider taking the lead in promoting these activities in cross-institute "Road Map" initiatives.

Research Strategies and Questions:

- Develop efficient data management software for integrating diverse high dimensional data sources.
- Develop new methodologies for querying and analyzing these multiple data sources, with a focus on integration of multiple data types to address critical hypotheses.
- Develop rigorous quality assurance protocols and standards.

B. Develop a battery of consistent measures, agreed upon by relevant research communities, to facilitate comparisons across studies of ocular diseases.

Research Needs and Opportunities: There is a need for the development of a battery of consistent measures, agreed upon by relevant research communities, to facilitate comparisons across studies of ocular diseases.

Research Strategies and Questions:

- Develop accepted descriptors (i.e., measurements) and methods for measuring them to support cross-study comparisons.

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Appendix A: The Full Progress Report

Progress Report

The contributions from epidemiological research in the past fifteen years since its last evaluation in an NEI strategic plan have advanced our understanding of the magnitude and impact in populations of the burden of blindness and visual impairment and the individual ocular diseases. Epidemiology has contributed significantly to our knowledge of risk factors for the major blinding diseases, and tested treatment and preventive interventions. Finally, epidemiological research has identified and evaluated health care delivery processes related to the ocular diseases and their consequences. The panel chose to highlight progress within the goals described above, reflecting the major blinding diseases and interventions.

Cataract

As the leading cause of blindness world wide, cataract should remain a primary focus for public health ophthalmology, in terms of prevention, better treatment strategies, and determination of disparities in access to surgical services. Highlights of progress include the following:

- Rigorous investigations into the etiology of cataract have been considerably enhanced by the development of valid and reliable classification systems to assess the presence and severity of different cataract types. Differentiation of nuclear, cortical, and posterior subcapsular (PSC) lens opacities is important, as it has permitted careful phenotypic description of the type of cataract and better characterization of the distribution of cataract types in populations which provide clues into possible etiological factors.

- Population-based studies in different racial and ethnic groups have suggested significant differences in the rates of specific cataract type. African Americans have a higher rate of cortical cataract compared to Caucasians, and lower rates of nuclear and PSC. Latinos appear to have higher rates of PSC cataract compared to rates in Caucasians, and PSC cataract rates also appear to be higher in Chinese persons.

- Sex differences in the prevalence of lens opacities have been found, with women having consistently higher rates of cortical opacities compared to men. There is less evidence for sex differences in nuclear or PSC cataract. Women are especially vulnerable to barriers for surgical care, and disparities in access to care have been found. The rates of blindness and visual loss due to cataract are significantly higher in women compared to men in many countries. Women have more difficulty accessing the resources necessary to obtain cataract surgery, and cataract campaigns are not designed to especially encourage women.

- The excess risk of cortical and PSC lens opacities in persons with diabetes appears to increase with increasing duration of diabetes. The level of control, as measured by levels of glycated hemoglobin, is related to both onset and progression of opacity. This research was key in determining the magnitude of the risk associated with diabetes, and for African Caribbean persons, the attributable risk of cortical cataract with diabetes is high, an estimated 14 percent.

- Ocular exposure to UVB in sunlight is a risk for cortical cataract. Methods to estimate ocular exposure in a more precise way were developed, and an evaluation in a population-based study demonstrated that, for all groups including women and African Americans, there is an increased risk of cortical opacity with increasing ocular exposure to UVB, even with the type of exposure found in a general population. The public health ramifications of this finding extend to global warming and the increase in lens opacity that might be attributable to the ozone hole have been modeled. However, exposure can be limited through very simple measures of wearing plastic glasses or sunglasses when outside, and wearing a brimmed hat. These measures have become part of the sun awareness campaigns carried out in numerous countries.

- The cataractogenic potential of some common medications has been identified. Inhaled steroids appear to be a risk factor for PSC, but also interestingly for nuclear opacity as well. A dose response relationship was reported, lending more weight to the association. While further confirmation is needed, these data suggest initial reports of no effect of inhaled steroids may be unjustified. Topical medications for lowering intraocular pressure have been implicated as risk factors for nuclear opacity in population based study and confirmed in clinical trials.

- A large and consistent body of literature has grown in support of the finding that smoking is a cause of nuclear cataract. Epidemiological research has demonstrated a dose response relationship, and smoking increases the incidence and progression of nuclear opacification. Smoking cessation appears to reduce the risk of cataract. The data are sufficiently compelling that cataract has now been added to the US Surgeon General's report on health effects of smoking, the first ocular condition to have this dubious distinction. An estimated 20 percent of cataract cases may be attributable to smoking in the US.

- The likelihood of a genetic pre-disposition to cataract has been evaluated in several population studies. In studies of twins, the heritability of nuclear cataract was estimated at 48 percent, with unique environmental factors estimated to account for another 14 percent of the variability. In cohort pedigrees that included smoking, the models suggest contributions from multiple genes, characteristic of a complex disorder. Similarly, there appears to be a strong genetic component to cortical cataract. In the twin study, additive and dominant genes accounted for 53-58 percent of the variability in cortical cataract, with unique environmental factors accounting for 26-37 percent.

- Health disparities in cataract surgery have been identified. African Americans are less likely to have cataract surgery, compared to Caucasians, despite having similar or higher rates of disability due to an opacified lens. The reasons for this health disparity are unknown. Language and financial barriers have been identified as impediments among Latinos in the United States who need cataract surgery.

- Outcomes research has resulted in several major findings. Even when surgical coverage improved under a World Bank program to increase coverage in India, epidemiological

assessments of outcomes showed that vision restoration was less than ideal, with the potential for higher rates of poor visual outcome in the rush to increase coverage. These findings were instrumental in program insistence on surgical audits to be certain that quality was not sacrificed for quantity.

- The use of large, simple trial methodology has demonstrated that medical testing before cataract surgery does not improve outcomes, and could be eliminated with cost savings. The use of large existing data bases have shown to be valuable resources for studies of small increased risks with changes in methods for cataract surgery, or investigating large population inequities in access to services where generalizability is important.

- A fascinating link between lens opacity and increased risk of early mortality has now been reported from several epidemiological studies. Nuclear opacity and mixed opacity in particular have been found to be independent risk factors for mortality, adjusted for health status, frailty, and other confounders. This association is clearly not causal, but suggests that the lens may well be a natural window into the aging process. This finding has been exploited by cell biologists interested in aging tissues, especially lens.

Age Related Macular Degeneration (AMD)

AMD is a leading cause of blindness in Caucasian population in the United States. A number of large population-based epidemiological studies have provided information regarding the prevalence and/or incidence of AMD and its relation to visual loss in whites of European ancestry, African Americans, and Hispanics. These data have provided estimates of prevalence in the United States population and documented the relatively high prevalence of AMD, especially in persons 75 years of age or older. While the prevalence of early AMD as manifest by retinal drusen is similar in the three racial ethnic groups, there is a higher incidence of late AMD, especially neovascular AMD in whites compared to Hispanics and African Americans. The reason for this is not known and future investigations into the cause are likely to be a rich source of new information.

Some of the progress made in epidemiology of AMD includes the following:

- While the prevalence is generally projected to increase due to more persons living to older ages in the population, there are new data suggesting that the incidence of AMD at a given age may actually be declining in the population. In the Beaver Dam Eye Study there was a lower 5-year incidence of early AMD in younger birth cohorts. For example, people examined when they were 70-74 years of age who had been born in 1913-17 had a 14 percent 5-year incidence of early AMD, those born in 1918-22 a 10 percent incidence, those born in 1923-37 a 6 percent incidence, and those born in1928-32 a 4 percent incidence. This needs to be replicated by others. We do not know whether differences in specific exposures account for these changes, but finding them may provide further insights into the pathogenesis of AMD and its prevention at an earlier stage.

- Risk factors for AMD: Family history and smoking are strongly associated with AMD. The relation with smoking has important public health implications because it is a

modifiable risk factor. Other factors, less consistently shown to be associated with AMD, include markers of inflammation (e.g., white blood cell count, C-reactive protein), markers of subclinical cardiovascular disease (e.g., intima-media thickness), cataract surgery, hypertension, heavy alcohol consumption, dietary factors, sedentary lifestyle, and obesity.

- Substantial progress has been made in understanding the genetic etiology of AMD. Two gene complexes with substantial individual and population effects have been identified (complement factor H (CFH) and HTRA serine peptidase 1 (*HTRA1/LOC387715*)). Another gene complex (Complement factor B (BF), and complement component 2 (C2)) with substantial individual effect has also been identified. Numerous other genes with smaller effects (e.g. *ABCA4, APOE, VEGF, HMCN1, VLDLR, LRP6*) have been associated with AMD in at least one dataset. Gene-environment interactions between *HTRA1/LOC387715* and smoking have been seen in several studies, as has an interaction between smoking and CFH in other studies. Interactions have also been seen with inflammatory biomarkers, e.g., C-reactive protein. One of the reasons for differences among populations and racial/ethnic groups is the differences in distributions of genetic variations associated with AMD. There have been very few population-based studies yet to examine these and other gene-environment interactions for AMD. Such studies may provide further insights regarding the pathogenesis and detection of those at risk of AMD.

- The Age-Related Eye Disease Study (AREDS), in which nearly 5,000 Americans at high risk for AMD were prescribed high doses of zinc and three antioxidant vitamins (C, E, and beta-carotene) showed that this treatment lowered the risk of developing advanced AMD by 25 percent and reduced the risk of vision loss caused by advanced AMD by 19 percent. Of the 1.3 million who are expected to develop late AMD, it is estimated that 300,000 of them would avoid it (and vision loss during the next 5 years), if they took the AREDS type supplement. Epidemiological evidence from the AREDS showed a protective association of dietary lutein/zeaxanthin and omega 3 fatty acids, which has provided part of the rationale for study of these supplements in a new randomized controlled clinical trial, the AREDS 2.

- The trials showing not only preservation of vision but improvement in vision with VEGF inhibition are a major advance. Studies of equivalent treatments but at a lower cost are important. To date there are no similar treatment that prevent visual loss from geographic atrophy once the central part of the macular is involved.

- There has also been progress in the development and application of unified tools for assessment of AMD, including the development and use of an international classification scheme for AMD, and development of new AMD severity scales to measure progression of disease.

Diabetic Retinopathy

Diabetic retinopathy remains a leading cause of blindness in the western world and the prevalence of diabetes is dramatically increasing. There has been important progress in understanding this disease, and developing methods to prevent blindness from diabetic retinopathy in the last 15 years, both because of the development of new approaches toward prevention and because of new treatment strategies. Highlights of progress include the following:

- Population-based studies have determined the magnitude of diabetic retinopathy among persons with diabetes, and the degree of vision loss. While it is clear that Latinos have an excess risk of type II diabetes compared to Caucasians, it is not clear that they have more diabetic retinopathy unrelated to poorer control and less access to care.

- Population-based longitudinal studies of a cohort of persons with Type I and type II diabetes have demonstrated the importance of glycemic control in onset and progression of diabetes. Subsequent clinical trial results from the Diabetes Control and Complications Trial and the United Kingdom Prevention of Diabetes Studies have demonstrated that the risk of diabetic retinopathy can be reduced by careful control of blood glucose and blood pressure. There is also suggestive evidence that careful control of serum lipids can reduce the risk of retinopathy.

- Economic analyses of the cost benefit of screening and treating diabetic retinopathy has shown the overall cost savings to be accrued by society in saving sight from diabetic eye disease. These analyses have been instrumental in gaining support for eye health education and further funding for better ways to screen for diabetic retinopathy in the community.

- Clinical trial results from the Diabetic Retinopathy Study, Diabetic Retinopathy Vitrectomy Study and the Early Treatment Diabetic Retinopathy Study have led to evidence-based clinical strategies for treating diabetic retinopathy. These strategies were developed from the treatment approaches used in these studies, which involved long-term follow-up in randomized clinical trials of thousands of patients. The studies demonstrated that widespread use of these treatment strategies would reduce the risk of blindness in persons with proliferative diabetic retinopathy by more than 90 percent.

Retinitis Pigmentosa

Retinitis pigmentosa (RP) belongs to a group of inherited retinal degenerations that results in the destruction of the photoreceptor cells and ultimately in loss of vision. An estimated 100,000 people in the United States have RP.

- An NEI-sponsored, randomized clinical trial concluded that vitamin A palmitate 15,000 IU/day, on average, slowed the course of disease among adults with typical RP. A second clinical trial found that docosahexaenoic acid (DHA) did not, on average, provide

additional therapeutic benefit for patients with RP receiving vitamin A. These trials have added much to our understanding of the value of nutritional supplementation in RP.

Glaucoma

Glaucoma is now the leading cause of irreversible blindness world wide and the second leading cause of blindness, behind cataract, in the world. Thus, it is critical that significant emphasis and resources continue to be contributed towards determining the pathophysiology and management of this disease. The past 15 years have provided significant data in these areas both in the U.S. and worldwide. Progress includes the following:

- Population-based studies in Baltimore, Barbados, Tucson, and Los Angeles demonstrate that persons of African ancestry have significantly higher prevalence of open-angle glaucoma compared to those of European ancestry, and high rates of glaucoma are also found in Latinos.

- Each of the population-based studies has found that 50-80 percent of persons with glaucoma in the community are previously undiagnosed. Elevated intraocular pressure (IOP), while a risk factor for glaucoma, is not a hallmark of the disease and cannot be sued on its own to screen for glaucomatous functional damage.

- Risk factors for open-angle glaucoma include age, family history, elevated intraocular pressure, ancestry, hypertension, myopia, and possibly diabetes mellitus. These studies have also confirmed some novel risk factors such as central corneal thickness, and ocular perfusion pressure.

- Case control studies have identified certain genes to be associated with glaucoma (*MYOC*, *OPTN*). However, population-based studies have not confirmed these data. Overall, few genes have been identified that would be associated with a significant proportion of persons with open-angle glaucoma.

- Clinical trials have validated the role of lowering IOP in the management of glaucoma, and treating persons with ocular hypertension. These trials have also identified risk factors for the development of glaucomatous damage.

Cornea

The area of cornea and external ocular surface disease is, by definition, a broad one, and highlights of the past 15 years have been in the following major areas: corneal infections, corneal transplantation, herpetic keratitis, and keratoconus. Ongoing studies seek to evaluate donor tissue age and corneal transplant outcomes. Progress includes the following:

- Case control studies of contact lens associated corneal infections identified patient and product related risk factors for these epidemics.

- -Past researchers report that donor-recipient tissue typing had no significant long-term effect on the success of corneal transplantation in more than 400 patients at high risk for rejection.

- In the area of *Herpes simplex virus (HSV)* stromal keratitis, patients who received topical corticosteroids experienced faster resolution of the stromal keratitis and fewer treatment failures. There was no apparent benefit in the addition of oral acyclovir to the treatment regimen of a topical corticosteroid and a topical antiviral. In the treatment of acute HSV epithelial keratitis, there was no benefit from the addition of oral acyclovir to treatment with topical antivirals in preventing the development of stromal keratitis or iritis. Acyclovir did, however, significantly reduce the recurrence of ocular herpetic infection.

- The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study, an observational study of keratoconus, characterized the disease and its progression and patients' prognosis, given modern treatment plans.

Refractive Error

Epidemiologic research funded by the NEI in the area of refractive error has been robust in the recent past. The research program has been focused in four major areas, and much of the emphasis has been specifically on myopia, rather than on refractive error in general: (1) prevalence of refractive error; (2) risk factors for myopia; (3) treatment of myopia; (4) genetic epidemiology of myopia. Highlights of progress include the following:

- Estimates of the prevalence of refractive error, including presbyopia, have resulted from a variety of studies in various countries. The prevalence of various types and degrees of refractive error in children worldwide have been compared and contrasted, too. These studies show general trends, including an increase in the prevalence of myopia during late childhood and early adolescence, a decrease in prevalence after age 50 years, and higher prevalences in urban compared to rural samples. Uncorrected refractive error has an impact on daily functioning, and uncorrected presbyopia appears to adversely affect even illiterate rural populations.

- Studies on predominantly Caucasian children have identified risk factors for the development of myopia that include a family history of myopia. The specific genetics of the likely complex disorder called myopia continue to be elusive but work is ongoing, and some genetic loci have been identified for high, familial myopia. Accommodative lag is greater in myopic children but is debatable as a risk factor for the onset of myopia, apparently depending on the method of measurement. The response AC/A ratio is elevated prior to myopia onset. Near work is associated with myopia, as is the degree of education.

- Clinical trials of treatment to slow the progression of myopia have been fruitful. Conventional bifocal spectacle lenses reduced myopic progression in school-aged esophores. In one trial progressive addition spectacle lenses showed a modest benefit in a group of children unselected for phoria status, but did not achieve a treatment effect

deemed clinically meaningful. When the children were parsed further, esophoric children with high degrees of accommodative lag showed a meaningful treatment effect. A randomized clinical trial of rigid gas-permeable contact lenses for control of juvenile onset myopia showed little clinically important effects. Intriguingly, most of the treatment effect across studies occurred only in the first year of three years of follow-up.

Pediatric Ophthalmology

Amblyopia
A research consortium has been established to efficiently undertake a number of treatment trials for amblyopia. The Pediatric Eye Disease Investigator Group (PEDIG) findings include the following:

- A daily atropine drop and part-time patching produced effects of similar magnitude in moderate strabismic, anisometropic and combined amblyopia in 3 to <7 year olds, suggesting that either atropine or part-time patching are both effective treatments. In a further study of atropine dose, PEDIG reported similar magnitude of treatment effect in weekend atropine (2 days a week) and daily atropine, suggesting that weekend atropine is a reasonable starting regime for atropine.

- In studies of patching dose, similar effects of prescribed patching 2 hours/day and prescribed 6 hours/day in moderate amblyopia were reported, and similar effects of prescribed 6 hours/day and prescribed full-time patching in severe amblyopia. These data suggest that a less intense starting regime of patching treatment is reasonable, reserving more intense regimes for resistant cases, and this is also consistent with other studies of the emotional impact of patching.

- Regarding the need for un-patched controls in studies of occlusion, a benefit of patching over glasses alone, and a benefit over no treatment, in unilateral visual acuity deficit was found. Patching appears better compared to continued glasses alone, after stabilization of visual acuity in glasses.

- In a study of older amblyopes, a higher response rate occurs in 7-<12 year-olds who were treated with patching (2 to 6hours/day) and daily atropine 1 percent drops, in addition to spectacles, compared with spectacles alone. In an even older cohort (13 to <17 year olds), the augmented treatment (patching 2 to 6 hrs/day), in addition to spectacles, was only more effective (than spectacles alone) in those that had not been treated previously. Nevertheless, the finding that up to a quarter of older children responded to either treatment suggests that plasticity of the visual system extends through the teenage years.

- With a prolonged spectacle run in period, it was found that about a quarter of anisometropic amblyopes had restoration of equal visual acuity without any addition patching or atropine treatment, and that over three quarters had an improvement in visual acuity. What is particularly surprising is that not only did patients with pure anisometropic amblyopia improve, but so did children with strabismic amblyopia.

Moreover, refractive correction alone resulted in a significant improvement in acuity in a group of children failing preschool vision screening, compared to no treatment.

- In a prospective observational study, the rate of regression of amblyopia was reported, risk factors for regression and a benefit to weaning treatment found if it was moderate or intense. All the above amblyopia studies have changed the approach to clinical amblyopia management.

Strabismus

- An observational study of congenital esotropia studied infants age 4 to < 20 weeks and at 28 to 32 weeks of age; a quarter of infants showed resolution, with most showing an intermittent or variable deviation at enrollment. Resolution occurred in only one of 42 cases that had a constant esotropia > or = 40 pd on both the baseline and first follow-up examination and had a refractive error < or = + 3.00 diopters. These data are important in defining which infants might benefit from earlier intervention.

Retinopathy of Prematurity

- Cryotherapy for threshold ROP markedly reduced the risk of profound vision loss, and lead to the widespread use of cryotherapy for that condition. A subsequent randomized trial used a risk model to define which infants were at increased risk for a poor outcome and then randomized infants to early versus conventional timed treatment. The study provided evidence that earlier treatment (now laser rather than cryotherapy) was beneficial in a subset of infants with more severe ROP, and has further changed the indications for and timing of treatment.

Screening for Pediatric Eye Disease

- The comparison of a variety of screening methods to each other and to 'gold standard' eye examinations, in an enriched population of 3- to 5-year olds (over-representing children who were likely to have ocular abnormalities), found several reasonable approaches. For detecting amblyopia, the autorefractor methods had a higher sensitivity than visual acuity screening methods using HOTV letter or Lea symbols, and photoscreener methods and stereoacuity screening tended to perform less well than visual acuity screening. In a second study, lay screeners and nurses performed as well as licensed eye care professionals.

Congenital Cataract

- The incidence of congenital and other forms of pediatric cataract have been reported by a number of groups in the US, UK and Scandinavia. Risk factors have been reported, though nearly all are difficult to modify such as older maternal age and low birth weight.

Population-based Studies on Prevalence of Pediatric Eye Disease

- Several research groups have studied defined populations to elucidate the burden of pediatric eye disease in communities, which can be generalized to larger populations. These data are important in determining the focus of future interventional studies. A study in the UK reported the cumulative incidence of amblyopia (decreased visual acuity due to anisometropia, strabismus, or sensory deprivation) and cumulative incidence of

strabismus. Population-based studies using comprehensive medial record retrieval in Olmsted County USA have provided cumulative prevalence data on esotropia, exotropia and hypertropia, defining the most common forms of each of these types of strabismus. Ongoing work in multi-ethnic and racial populations in Los Angeles and Baltimore are underway.

Infectious Diseases

Infectious eye disease is still a leading cause of avoidable blindness world wide, and the NEI has a long history of research support for control of these conditions. The epidemiology efforts have been focused on trachoma and the ocular complications of AIDS. Both areas have been highly successful. Each is described in turn:

Trachoma

Caused by repeated episodes of ocular *Chlamydia trachomatis* infection, trachoma is the leading infectious cause of blindness world wide. With a donation program of azithromycin, global efforts to eliminate blinding trachoma have been intensified. The World Health Organization has endorsed a multi-faceted control strategy, SAFE, consisting of Surgery (to correct trichiasis), Antibiotics (to decrease the community pool of infection, Face washing and Environmental change (to interrupt transmission). Considerable research progress in trachoma has been made, and only the highlights are summarized below:

- A randomized trial in Ethiopia has found that a single dose of azithromycin following surgery for trichiasis reduced recurrence by 30 percent compared to topical tetracycline. With good training and certification of non-ophthalmologist trichiasis surgeons, the recurrence rate can be as low as 10 percent at one year. Trichiasis surgery appears to improve visual acuity by 0.13 LogMAR, and improves the quality of life of patients post operatively. The recurrence rates following surgery are highly variable, and in part reflect surgeon skill.

- While considerable work has been carried out on flies as a physical vector for trachoma, it is one of only many routes of transmission. In The Gambia, a randomized community controlled trial of an intense fly-spray program reduced trachoma in intervention compared to controls villages, but had no effect on either trachoma or infection in Tanzania where the prevalence is higher.

- With community based longitudinal studies of infection and disease using sensitive polymerase chain reaction (PCR) based laboratory techniques for detection of chlamydia, several studies have shown that immediately after treatment, infection rates in these communities drop drastically, but rates of trachoma lag far behind. Even by one year, there is only modest decline in follicular trachoma, although severe trachoma is a more sensitive marker of the drop in infection. These data are critical for national programs, as they continue to provide mass treatment for communities based on rates of clinical trachoma, not on infection rates.

- Despite initial promise that repeated community based mass treatment with antibiotics may lead to elimination of infection and reduction of trachoma, experience in Tanzania

and Ethiopia suggests that re-emergence of infection and disease after treatment cessation is an issue. In The Gambian studies, infection is brought back from outside the villages during pilgrimages, but in Tanzania, re-emergence appears to come from children with heavy bacterial loads for whom a single yearly dose may be inadequate. Modeling efforts to determine optimal frequency and coverage of dosing with azithromycin in hyper-endemic communities has been carried out, but need longer term empirical data to fully predict success.

- Mass azithromycin administration does not appear to result in resistant strains of either chlamydia or other bacteria over time, which is important for countries facing many years of yearly mass treatment to eliminate blinding trachoma.

- Operational research in several countries has confirmed the association of facial cleanliness with less trachoma, strengthening the evidence base for inclusion of hygiene and environmental change components of country trachoma control programs.

Ocular complications of AIDS

With the onset of the AIDS epidemic in the 1980's, there was an associated epidemic of cytomegalovirus (CMV) retinitis, which by the early 1990's had become the most common intraocular infection at major urban centers in the United States and possibly in the United States as a whole. A consortium, the Studies of the Ocular Complications of AIDS (SOCA), has been productive in determining appropriate treatment; studies using data from more than one trial in this consortium were important in describing the course of CMV retinitis in the pre-HAART era for comparison with the effects of highly active antiretroviral therapy (HAART). The cohort study of patients with AIDS is a unique resource because it contains ophthalmic data over time and includes patients with AIDS from all risk groups for HIV infection. The results of these studies are summarized below:

- Demonstrated that ganciclovir and foscarnet were equivalent for controlling CMV retinitis and produced similar visual outcomes, but that foscarnet therapy was associated with a lower mortality due to a modest antiretroviral effect. This study established foscarnet as a reasonable option for the treatment of CMV retinitis.

- Established standardized methods for evaluating CMV retinitis and its outcomes, methods which are still in use today.

- Described the course of treated CMV retinitis and the incidence of and risk factors for its complications.

- Demonstrated that combination therapy was superior to monotherapy for the treatment of relapsed retinitis.

- Demonstrated that the then popular approach of switching from one anti-CMV therapy to another for relapse of the retinitis (in the absence of demonstrated CMV resistance) was no better than reinduction with the same drug.

- Established the efficacy of cidofovir (HPMPC) for the treatment of CMV retinitis.

- Described the long-term side effects and reversibility of the side effects of cidofovir.

- Demonstrated that a monoclonal antibody to CMV used as adjunct therapy to anti-CMV drugs (which preliminary uncontrolled data suggested might be effective and relatively non-toxic) was ineffective and associated with a higher mortality.

- Demonstrated that systemic therapy with cidofovir was equivalent to a regimen of the ganciclovir implant and oral ganciclovir for controlling retinitis and preventing visual loss.

- Described the surgical complications of ganciclovir implant surgery.

- Description of the characteristics of patients with new-onset CMV retinitis in the HAART era. These patients are largely HAART experienced and will need long-term anti-CMV therapy.

- Description of the course of CMV retinitis in the HAART era. Even among patients with immune recovery there is a surprisingly high rate of CMV retinitis relapse, higher than anticipated. Therefore, these patients need ongoing ophthalmologic monitoring. Guidelines were formulated for inclusion in the U.S. Public Health Service Recommendations on the Treatment of Opportunistic Infections in Patients with AIDS.

- Evaluation of the rates and causes of visual loss of patients with AIDS in the HAART era, both among those with and without CMV retinitis. A higher than expected incidence of cataract was discovered, even among those without CMV retinitis.

- Evaluation of immune recovery uveitis (IRU), which is an inflammatory response to CMV in the eye that occurs as the immune system recovers as a consequence of HAART. IRU is associated with structural complications in the eye and visual impairment. Risk factors were described.

- Evaluation of risk factors for mortality among patients with AIDS, documenting the increased risk of mortality among those with CMV retinitis and the beneficial effect of immune recovery.

- Improved understanding of the specific immune responses to CMV responsible for controlling CMV retinitis without anti-CMV therapy after immune recovery.

- Description of ocular problems among patients with AIDS without ocular opportunistic infections (OIs), including the presumed HIV-related neuron-retinal disorder (HIV-NRD), manifested by decreased contrast sensitivity (often sufficient to impair reading speed) and abnormal perimetry. HIV-NRD appears to be more common among women and non-whites.

- Studies on resistant CMV, including the description of the effect of HAART on the incidence of resistant CMV (a reduction by ~2/3) and risk factors for resistant CMV in the HAART era, and the description of the incidence of resistant CMV, which in the pre-HAART era was 0.25/person-year (PY) for each drug, and the course of resistance. Evaluation of the molecular genetics of resistant CMV and correlation with CMV phenotype has been done for both ganciclovir and foscarnet. Evaluation of the clinical outcomes of resistant CMV has demonstrated that resistant CMV identified in the blood was associated with worse clinical outcomes. However, evaluation of the amount of CMV DNA in the blood (CMV viral load) as a marker for resistant CMV, due to its poor positive predictive value, was not clinically useful. Evaluation of direct PCR amplification and sequencing of blood specimens to identify patients who harbor resistant CMV is potentially more useful. Because typical resistance testing requires several weeks to perform (CMV must be isolated from cultures and tested for susceptibility or mutations) it had limited clinical utility. However, direct PCR amplification and sequencing can be performed in < 48 hours, making it potentially clinically useful. There typically was >90 percent agreement between the two methods, and the more rapid method correlated with clinical behavior, making it a clinically useful approach.

Health Services Research

Traditionally, the NEI has funded limited research into eye health services but recent demonstrations of disparities in rates of vision loss and better appreciation of research into potential economic trade-offs have made this area of inquiry more prominent. Ophthalmic epidemiology has contributed to this field, as part of collaborative efforts, in the following advances.

Development of Outcomes Relative to Patient-centered Perspectives

- Elements of this work include 1) development of patient-derived functioning questionnaires such as the VAQ, ADVS, and VF-14 (among others) and the subsequent creation of the NEI-VFQ; 2) greater use and understanding of analytical methods for patient reported functioning, such as Rasch analysis and interval scaling; 3) better characterization of the role of vision and other factors in assessment of self report and performance based measures of overall patient functioning; 4) greater understanding and application of analysis of patient preferences, generally expressed as “utilities”; 5) application of qualitative research techniques such as the use of focus groups to assess patient preferences for care and difficulties with care utilization.

Improved Understanding Value of Health Care Services

- With the data from the new tools and measures, the ability of new (and traditional) interventions to improve patient functioning complements improvement in traditional endpoints of effectiveness. In addition, application of statistical modeling techniques can reveal the impact of vision on not only the costs to society but also the costs savings associated with better use of eye care services, as has been demonstrated for cataract surgery and laser treatment for diabetic retinopathy.

- In collaboration with experts in the application of econometric techniques, research has shown an association between more frequent use of regular eye exams among the elderly and a reduced rate of development of new instrumental activities of daily living (IADL) and activities of daily living (ADL) limitations.

Identifying How to Improve Outcomes of Care by Better Application of Evidence-Based Medicine and RCT Findings

- A large, simple, randomized trial of medical testing prior to cataract surgery found no difference in patient morbidity or mortality, suggesting that costs of cataract surgery could be reduced if such testing were eliminated.

- A massive design for eye care services in Australia, rooted in evidence based practices and public health approaches, has been created showing economic value to society and cost savings. This collaboration of epidemiologists, ophthalmologists, economists, and rehabilitation specialists has set a standard for national programs approaches.

- Several epidemiological studies have identified disparities in population use of established eye care approaches to reduction of visual loss. African Americans have more visual loss from cataract, and use less cataract surgical services. Many Latinos with diabetes do not have regular eye exams, in part due to language barriers and financial hardships. Those with diabetes in rural areas, and those cared for by general practitioners, are less likely to have regular eye exams. Quantitative and qualitative research techniques are used to identify factors associated with poorer outcomes, as well as less frequent use of eye care and other health care services.

- These and other studies have supported the importance of looking at a variety of factors in ensuring better implementation of evidence-based and RCT findings. These factors include: 1) patients; 2) their support systems; 3) providers; 4) health system structures and financing; and 5) complex interactions across all of the prior elements.

- Several studies have identified significant variation in the provision of care by eye care providers for major eye conditions, creating the need to better understand the factors that influence provider performance and how to assist in implementing best evidence medicine.

Overarching Methodology

Current Methods Used for Mapping Genes Associated with Ocular Diseases

Ophthalmology makes tremendous use of innovative genetic studies geared towards describing the interplay between environmental and genetic factors that contribute to the development of either single-gene or polygenic (multifactor) ocular diseases. A combination of powerful and flexible statistical methods together with a detailed understanding of the molecular forces directing the mechanisms of new mutations is essential in describing the genetic factors conferring susceptibility or resistance, affecting the severity or progression of ocular diseases, and in further characterizing the range of environmental influences that contribute to the elevation of such risks.

Depending on the type of available clinical data, numerous genetic study approaches are being implemented, each with its own advantages and disadvantages. However, great progress has been obtained through the interlink between the different findings of all such methods. One of the most frequent techniques conducted for mapping ocular susceptible genes is based on gathering family disease and environmental history across two or three generations, and on collecting DNA samples that are then analyzed as part of "linkage analysis" computational methods. This strategy is focused on detecting whether a certain set of genes occurs more frequently than would be expected by chance, namely with a preponderance in the diseased population versus the population at large. However, there are challenges involved in this sort of study, mostly due to the sometimes missing parental genotypes, due to partially informative families (deceased relatives), and to insufficient information describing possible environmental factors that modify susceptibility to illness.

An alternative approach is based on "association studies", a complementary strategy for detecting complex disease susceptibility genes. The advantage of this technique is the use of population-based rather than family-based DNA. A nonrandom association of alleles represents disequilibrium between closely linked genetic loci, a genetic set that usually dissipates slowly over successive generations even in a large set population. This particular information genetically differentiates the affected and non-affected individuals. However, careful clinical design is usually taken to ensure a correct matching for ethnicity or other factors that may contribute to genetic differences. For example, population stratification due to recent admixture of different populations or inappropriate matching of patients and controls may falsely affect these results. Nevertheless, these problems are circumvented with the family-based study designs.

Another strategy complementing association studies is based on searching for an increased prevalence of a particular functional genetic variant among cases. This aim is accomplished by searching for differences in the frequency of a gene allele between a sample of patients and controls, a result that will directly implicate a gene as influencing ocular disease susceptibility. Needless to say, both family and population oriented studies are complementary and useful in summarizing the total number of genetic mutations that affect a given disease.

In concert with the different statistical algorithms and clinical designs we are also benefiting from the recent molecular laboratory technological advances that have enabled the genotyping of hundreds of thousands of genetic alleles on a single chip. While nowadays we are provided with an extraordinary collection of genetic information, scientists are nevertheless posed with the challenge of producing innovative and novel analytic methods that will efficiently incorporate the full range of information being generated. Moreover, the inherent biologic complexity of complex ocular diseases necessitates a critical need for cooperation between molecular and computational researchers, without which novel discoveries and insights into the biological underpinnings of complex diseases will nevertheless lag and further impede a whole understanding of the underlying mechanisms.

Meta Data Analyses: Combining Information from Multiple Data Sources
In a recent paper by Samsa, Hu and Root (Journal of Biomedicine and Biotechnology, 2005:2, 113-123) a method is proposed for combining the results of composite relative risks due to the issue of risk factor colinearity and heterogeneity of the different cohorts. As stated by the authors, "creating multivariable regression models containing partial regression coefficients is central to the practice of epidemiology. Combining partial regression coefficients across datasets is difficult when the correlations among the risk factors in question are moderate to strong." The univariable synthesis method proposed by the authors has the advantage that correlations among the predictors are explicitly considered in the quantitative estimation of the partial regression coefficients.

Strategies for Conducting Gene-Environment Studies in Ocular Disease
Investigations of interactions capitalize on traditional epidemiologic study designs, with the case-control and case-only the most widely used. In the traditional case-control design, the exposure of interest is compared among the cases (diseased individuals) and controls and the odds ratio tabulated reflecting the relative effect of the exposure (the gene) on disease. This can be easily expanded to incorporate risk due to a third, here environmental, risk factor. The case-only design uses only diseased individuals and examines the association between genetic and environmental measures and an odds ratio is again calculated. While more powerful in detecting an interaction, the case-only design is only valid in the absence of gene-environment association. Said differently, the genetic and environmental factors examine must be independent.

The study designs described above can and have been implemented in various ways. For diseases with established lifestyle or environmental risks, research addressing interaction has focused on identification of genes that differentially effect risk for disease. Genes of interest are generally chosen based on their relationship with the known environmental factor. Such an approach may be useful in diabetic retinopathy where glycemic control and blood pressure have been shown to be important. Examination of genes that relate to these risks may prove to be important in interactions and disease progression. In contrast, for diseases with known genetic risk factors, examination of environmental risk factors has been of great interest. Following identification of candidate genes, generally from linkage and cloning studies, specific variants may then be associated with environmental risk factors. For example, recent work has examined interactions between smoking behavior, body-mass index, and risk genes for AMD. However, studies designed to specifically detect gene-environment interactions can also be used to identify new genes for disease. Segregation analyses, examination of affected sibling pairs, and genome-wide association studies can all be adapted to take environmental exposure variables into account and focus results on the detection of genes which are involved in a gene-environment interaction. Segregation analysis and the use of affected sibling pairs will capitalize on differences in the environmental exposure of interested among individuals with disease. Similarly, genome-wide association tests can be calculated to test the joint effect of marker and environmental exposure on disease risk.

Appendix B: Objectives Already in the NEI Strategic Plan, *National Plan for Eye and Vision Research (2004)*

Retinal Diseases Program

- Continue to develop and test noninvasive technologies such as functional magnetic resonance imaging (fMRI), optical coherence tomography (OCT), adaptive optics, and confocal imaging to better understand retinal function and changes in retinal disease states.
- Study the interacting roles of the environment and genetics in risk factors for retinal diseases.
- Explore the pathophysiological heterogeneity of AMD to hasten the development of the tools needed for improved diagnosis, prevention, and treatment.
- Standardization of the definitions and characteristics of retinal phenotypes in macular disease. This will allow more precise disease definitions based on genotype-phenotype – environment correlations for the study of disease progression and response to therapy.
- Development of diagnostic methods and therapeutic approaches to distinguish among infectious, immunopathogenic, and autoimmune posterior segment inflammation.

Corneal Diseases Program

- Gain an understanding of the epidemiology of and risk factors for infectious and inflammatory corneal and ocular surface diseases to develop preventive strategies.

Lens and Cataract Program

- Determine the extent of visual impairment due to cataract, especially in underserved populations, in the United States and world wide.
- Apply population genetics to identify gene-environment interactions that may confer susceptibility to age-related cataract.

Glaucoma and Optic Neuropathies Program

- Elucidate the prevalence, pathophysiology, natural history, and history of intervention results of optic neuropathies such as glaucoma and optic neuritis over full time course of these diseases and within ethnic subgroups.
- Develop improved diagnostic measures to detect optic nerve diseases onset, progression, and treatment effectiveness including development and validation of predictive genetic testing.

Strabismus, Amblyopia, and Visual Processing Program

- Identify the human risk factors environmental and genetic for myopia and abnormal eye growth.

- Evaluate the efficacy of potential approaches special spectacles and contact lenses for slowing the progression of myopia.
- Translate knowledge into tests for reliable screening and early diagnosis.

Low Vision and Blindness Rehabilitation

- Evaluate the effectiveness of existing rehabilitation strategies and programs and assess their impact on task performance, psychosocial and psychological factors and quality of life parameters in people with visual impairment.
- Develop and understanding of visual and non-visual requirements for performing everyday tasks. Develop comprehensive definitions of visual disabilities.
- Develop an understanding of perceptual and cognitive factors involved in the performance of everyday tasks such as driving, other forms of mobility, and reading.