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Perspective

Translational Epidemiology in Ophthalmology: From Etiologic Research to Personalized Health Impact

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Epidemiology is the study of the distribution and patterns of health characteristics and their causes in well-defined populations. Over the last few decades, well-designed traditional epidemiologic studies have defined the prevalence of and elucidated risk factors for eye diseases such as cataract, refractive error, open-angle glaucoma, age-related macular degeneration, and diabetic retinopathy. These discoveries into the etiology of eye diseases have facilitated the understanding of pathogenic mechanisms, the modification of risk factors to prevent disease, and the identification of high-risk individuals for therapeutic interventions.

In recent years, epidemiologic research has played a crucial role in translating scientific discoveries into strategies that will be aimed at reducing the burden of vision loss both at the population and patient levels.[1] In a commentary in the *American Journal of Epidemiology*, Khoury, Gwinn, and Ioannidis describe the different phases of translation, from discovery to population health impact.[1] At the initial stage, epidemiologic studies can explore the role of a basic scientific discovery (eg, a disease risk factor or biomarker) in developing a "candidate application" for use in practice (eg, assessing sensitivity and specificity of a test) in observational etiologic studies such as cohort or case-control studies. Prediction models may be developed to identify high-risk individuals who might develop severe disease and benefit from further interventions. Subsequently, epidemiology can be used as a tool to evaluate the efficacy of a candidate application or the effectiveness of interventions on population health outcomes in randomized controlled trials (eg, assessing clinical utility in improving health outcomes). The practice of epidemiology can help to assess the implementation and dissemination of guidelines into clinical practice. The term "translational epidemiology" has been coined to describe the application of epidemiologic methods in all phases of translational research.[1] Translational epidemiology has advanced within the field of ophthalmology due to progress made in the following key areas: (1) ocular imaging, (2) genomics, (3) proteomics, and (4) medical devices.

First, eye fundus imaging is useful to document its status and to assess any changes from a healthy condition. In addition to the diagnosis of ocular disease, retinal imaging also allows for the detection, diagnosis, and management of hypertensive and cardiovascular diseases.[2] In the last few decades, ocular imaging has rapidly advanced from simple fundoscopy to fundus photography to more advanced imaging modalities. Imaging can focus on the retinal structure or on a particular functional aspect of the retina, or on a correlation of the two. Retinal imaging has increased the accuracy of diagnostic and screening criteria for open-angle glaucoma, cataract, pathologic myopia, diabetic retinopathy, and age-related macular degeneration in epidemiologic studies. It also has facilitated the development of classification and grading systems for these eye diseases, including the

Wisconsin Age-Related Maculopathy Grading System, the Early Treatment Diabetic Retinopathy Study severity scale, and the Wisconsin Cataract Grading System. The development of these systems has further helped to standardize classification of these diseases and to distinguish between different stages of disease. Finally, the implementation of these systems allows the evaluation of the reliability and validity of different imaging techniques. The different options for fundus imaging are manifold, including computed tomography scan, scanning laser ophthalmoscopy, magnetic resonance imaging study, ultrasound imaging, infrared thermography, hyper-spectral imaging, color Doppler imaging, and photo-acoustic ophthalmoscopy.[2,3] These advances allow images to be sent to reading centers for manual or automatic screening and diagnosis (tele-ophthalmology). In fact, several groups worldwide are pursuing research to find the best and most accurate automatic systems for disease grading, including for cataract and diabetic retinopathy.[2] In addition, research is underway to attempt to extract as much information as possible from digital images to provide information on the structure and function of the human retina and to improve knowledge about the changes in the diseased retina at the earliest possible stage.[2,3] These advances in imaging modalities would allow a more precise and early diagnosis, implementation of more personalized therapies, and more accurate evaluation of treatment effects.

Second, the advances in the field of genetics during the past decade have provided insight into the molecular processes underlying several eye diseases. Using information from the Human Genome Project, researchers have made considerable progress, with approximately 1000 genes being discovered that may be associated with different ocular diseases. Many of these genes are responsible for rare diseases, but several recent discoveries using the large-scale genome-wide association approach have identified genes that contribute to common age-related eye diseases, including age-related macular degeneration, open-angle glaucoma, and myopia.[4,5] To elucidate further the pathophysiology of these common eye diseases, efforts are underway to examine gene-gene and gene-environment interactions. However, these efforts are hampered by limited statistical power of traditional study designs.[6,7]

In coming years, genetic epidemiology will play an important role in developing new methodologic approaches to tackle these limitations. In order to facilitate application of genetic risk prediction in clinical research and, in the future, in clinical practice, efforts are underway to combine all known loci for a particular disease or set of diseases onto one genotyping array.[8] Moreover, dense genotyping on such arrays ensures that the causal variants can be better localized. Such causal variants typically have larger effect sizes, thus further improving risk prediction.[8] Although comprehensive evaluations for all ocular diseases are not yet possible, progress has been made and efforts are ongoing to explore the possibilities for implementing human genome information in important clinical problems in ophthalmology.[8]

Advances in molecular genetics also have helped identify several gene defects responsible for retinal dystrophies including mutations in the *RPE65*, *AIPL1*, and *GUCY2D* genes in Leber congenital amaurosis (LCA), in the *RPGR* gene in X-linked retinitis pigmentosa, and the *ABCA4* gene in Stargardt disease.[9] These advances combined with progress in gene transfer technologies have led to the first human clinical trials of gene therapy. Three separate phase I/II trials assessed the safety and efficacy of subretinal recombinant adeno-associated virus mediated therapy for patients with *RPE65*–deficient LCA.[9] These studies show encouraging safety and functional results. The initial results may provide further insights into the safety and efficacy of gene therapy for a range of currently untreatable eye disorders.

Third, proteomics studys the structure and function of proteins. Currently there is a lack of molecular biomarkers that will facilitate disease categorization, monitoring of disease progression, and treatment efficacy. An important limiting factor in ophthalmology is the lack of validated preclinical models to study eye disease.[10] Although animal models are valuable preclinical tools to investigate complex disorders, certain ocular signs and symptoms are difficult to model in organisms and, therefore, only specific features that are conserved across species and extrapolated to human beings can be investigated. In this regard, efforts are underway to develop a map of the human proteome that identifies novel protein families, protein interactions, and signaling pathways.[10] Proteomic technologies such as gel electrophoresis, liquid chromatography, mass spectrometry, protein microarrays and bioinformatics will play an important role in drug discovery, diagnostics, and molecular medicine because they link genes, proteins, and disease. As researchers study defective proteins that cause particular diseases, study findings will help develop new drugs that either alter the shape of a

defective protein or mimic one that is missing. Identifying unique patterns of protein expression or biomarkers that are associated with specific diseases is promising. Unfortunately, many single-protein biomarkers have proven to be unreliable. Researchers are now developing diagnostic tests that simultaneously analyze the expression of multiple proteins thereby improving the specificity and sensitivity of these types of assays.[10] The first major application is likely to be in the detection and early diagnosis of eye diseases. Here, too, the application of epidemiologic principles in designing the studies and analyzing the data will allow the proper assessment of these proteomic assays.[11] Advances in proteomics will aid scientists in eventually developing medications that are personalized for different individuals, resulting in increased effectiveness and fewer side effects.

Fourth and finally, major efforts are underway in proof-of-concept and proof-of-value clinical trials to develop novel medical devices that may limit the burden of functional vision loss, including retinal prosthetic devices and multi-zone contact lenses to decrease myopia progression.[12,13] For example, for retinal degeneration, a chip can functionally take the place of dying or dead photoreceptor cells. The two approaches that are furthest along in development are subretinal and epiretinal implants. Thus far, phase I and II clinical trials with small sample sizes are showing varying results in terms of efficacy and safety of these devices.[12] Major challenges still remain: long-term safety for both the human subject and the electronic implant must be proved, and long-term efficacy must be demonstrated conclusively.[12] Refinement must occur in testing procedures, including psychophysical tests, as well as the application of tests such as optical coherence tomography and electrophysiologic recordings from the retina and brain that demonstrate not only *vision* at the retinal level but also in cognitive centers in the brain.[12]

Ultimately, the application of translational epidemiology in ophthalmology will lead to personalized medicine that will use specific screening and diagnostic testing to establish a precise diagnosis and determine the class of medications or methods of treatment to which a patient will best respond.[14] This integrated and multidisciplinary personalized approach has two important outcomes: first, the patient would experience less morbidity (i.e., blindness) because the most effective treatment would be selected initially; and second, making the correct therapeutic decision would save resources that are spent on ineffective therapies. Further translation of bench discoveries to the bedside in these key areas of research in ophthalmology may culminate in clinical benefits to patients and a decrease in the occurrence of vision-threatening eye diseases.

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