Insights into the Field of Ophthalmology in Precision Medicine

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A Paradigm Shift

Precision medicine (PM) is shifting the health care paradigm. Whereas the primary focus continues to be on treating disease, health care professionals are steadily moving towards preventive care through employment of this tailored medical practice. Predictive genomics and digital health are two dominant practices within PM. Understandably, PM was initiated to address cancer treatment and prevention (see **Precision Medicine Series: Oncology**, Julie Cramer, PhD). However the ophthalmic field is making notable gains in addressing preventive blindness through predictive genomics and digital health.

The Government Initiative

After announcement of "The Precision Medicine Initiative" in the 2015 State of the Union Address, the National Institutes of Health (NIH) responded the following year by recruitment of a 1 million+ people to take part in longitudinal studies that would determine how patient data and environmental factors can interact to cause disease. Under this program, blood samples for genomic analysis and storage, electronic medical records, lifestyle, and environmental data over a longitudinal period have been sent to a federal "biobank." This biobank continues to be analyzed to reveal previously unknown and unsuspected relationships among genomic, health history, behavior/lifestyle, and environmental factors in the risk or onset of disease. This initiative has found broad appeal between the medical disciplines, including ophthalmology.

Two Main Drivers

To many in the field, the doctrine of PM comprises four "rights": for the "right" patient dispensing the "right" medicine, at the "right" time, in the ""right" way (Lesko, 2013). It began with pharmacogenomic studies designed to tailor drugs to an individual patient's genetic make-up (Pirmohamed, 2011). This effort has since accelerated next-generation sequencing technologies (Hu et al., 2021; Schuler et al., 2022), cellular and molecular therapies in response to rapid advances in small molecule drugs (Jiang et al., 2021), autologous stem cell technologies (Karagiannis et al., 2019), and -omics (Li et al., 2021). The main drivers of PM are predictive genomics and digital health, where both have evolving regulatory processes (to be discussed in a future article in this series, **Precision Medicine: Regulatory Process**, by Alethea Wieland, CRS President).

The basis of predictive genomics is the human genome, where the $2.7 billion Human Genome Project (1990-2003) sequenced ~20,500 human genes. Thereafter, scientists easily identified causative genes of disease and their development. They also uncovered why specific individuals had an increased genetic predisposition to particular health conditions (e.g., cardiovascular disease, diabetes), and described the traits of certain diseases (i.e., in particular individuals why some cancers develop more aggressively, why some methods of chemotherapy are unresponsive, or they can survive longer carrying HIV). Therefore, predictive genomics can recognize a disease long before symptoms appear.

Digital health encompasses a wide range of categories including health information technology (health IT), mobile health (e.g., remote patient monitoring, or point of care testing), telehealth and telemedicine, wearable devices, and PM. Through medical apps and software that support clinical decisions doctors make every day to artificial intelligence (AI) and machine learning (ML), digital technology is boosting a health care transformation. This is because digital health tools have considerable potential in enhancing accurate diagnoses, treating disease, and improving delivery of individual health care.

The Need in Ophthalmology

PM is currently at the forefront of medical advancements that has steered the nation's medical research agencies to fund this rapidly growing area (Ginsburg & Phillips, 2018). With an estimated cost of $1 billion to put a new medicine on the market, it is imperative to develop patient-tailored treatments and medicines likely to succeed with reduced risk. Early detection enables administration of efficient treatments that prevent patient suffering and inflated healthcare costs. The field of ophthalmology has answered this need with past and present innovations described below.

Predictive Genomics in Ophthalmology

Genome-wide association studies (GWAS) were used to identify genetic loci for ocular conditions. The first successful GWAS was for age-related macular degeneration (ARMD), implicating complement factor H (CFH) (Haines et al., 2005), after which an additional 26 loci have been found through this method (Priya et al., 2012). Next, whole-exome sequencing (WES) and whole genome sequencing (WGS) have been employed effectively in identifying ~15 contributory genes or loci to ocular disorders ranging from macular dystrophy to primary congenital glaucoma. Array comparative genomic hybridization (aCGH) has been efficient in ophthalmic cases such as Cat Eye Syndrome (CES) with a deletion in 22q11 (Tzetis et al., 2012) to Reiger syndrome with a deletion in chromosome 4 (Moreira et al., 2010). Multiplex ligation-dependent probe amplification (MLPA) is a multiplex assay to detect copy number variations in genomic DNA sequences that has been accurate in identifying a number of genes and chromosomal loci responsible for ocular disorders, e.g., PAX6 deletions in aniridia (Wawrocka et al., 2013). For gene panels, a panel has so far been arranged for Leber's Congenital Amaurosis (Pomares et al., 2010). New genetic test panels for eye diseases can improve their diagnostic and prognostic accuracy, and in the process efficiently identify presymptomatic individuals who need preventive therapy or need to be monitored frequently for early signs and symptoms of a treatable condition (Shivapurkar et al., 2007).

Digital Health in Ophthalmology

Digital health has addressed four ocular conditions: glaucoma, myopia, ARMD, and diabetic retinopathy (DR). The Scoring Tool for Assessing Risk (STAR) glaucoma prediction calculators have been employed to estimate risks over five years for patients with ocular hypertension progressing to glaucoma (Medeiros et al., 2005). Refraction data from the Guangzhou Twins Eye Study, over a longitudinal follow-up, indicated the possibility in predicting and quantifying risk of pediatric high myopia (Chen et al., 2016). Comparable models may serve as clinical decision tools for evaluating whether alternative treatments, such as orthokeratology or topical atropine, are appropriate. Digitalization strategies and developments are currently ongoing and underway to ensure early detection, stability, and visual improvement in patients suffering from ARMD in the COVID-19 era (Sim et al., 2021). Recently, AI technology was brought to the bedside in addressing diabetic retinopathy (Ruamviboonsuk et al., 2022). Designing an optimal model of ophthalmic care to harness AI is still in its infancy.

SUMMARY

Through careful and steady progress, the field of ophthalmology has adequately brought precision medicine to the field. With increasing intensity of research in the field, through well-funded programs both intramural and extramural, the future looks bright for PM in ophthalmology. This is important nationally as recent surveys point to blindness being the third-most-feared condition in the U.S. behind cancer and AIDS.

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Dr. Chauhan earned his doctorate from Oxford University in Molecular Virology, where he conducted early studies in the generation of the now established baculovirus expression system employed for viral vaccines and gene therapy vectors. He came to the U.S. where he has spent the last 22 years on ocular and rare disease research yielding more than 20 peer-reviewed papers, numerous national and international presentations at research conferences, and acting as a reviewer of scientific manuscripts and grants.

At the Albert Einstein College of Medicine in New York, his research focused on cataracts, conducting both gene regulation and high-throughput gene expression analyses. While at the nationally leading Cincinnati Children's Research Foundation, he focused on development of eye tissues important in understanding congenital ocular diseases, where he primarily utilized transgenic mouse models of eye disease with state of the art imaging devices to probe the molecular and cellular biology of anterior ocular diseases. Dr. Chauhan worked at the UPMC Children's Hospital of Pittsburgh to translate his basic research to the bedside by primarily performing studies on human tissues.

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