Keynote Lecture II

Human DNA Sequence Variation and Improved Clinical Outcomes

David R Cox MD PhD

Biotherapeutics and Bioinnovation Center, Pfizer Inc., South San Francisco, CA, USA

.....

Dr Cox is internationally recognized for his research on the molecular basis of human genetic disease.

After receiving his BA and MS degrees from Brown University in Rhode Island, Dr Cox obtained his MD and PhD degrees from the University of Washington, Seattle. He then completed his Pediatric Residency at the Yale-New Haven Hospital in New Haven, Connecticut and was a Fellow in both genetics and pediatrics at the University of California San Francisco. From 1980 to 1993, Dr Cox held faculty positions in the Departments of Pediatrics, Biochemistry and Psychiatry at the University of California, San Francisco. In 1993, he accepted a position as a Professor of Genetics and Pediatrics at the Stanford University School of Medicine as well as the Co-director of the Stanford Genome Center. From 2000 to 2008, Dr Cox was the Chief Scientific Officer of Perlegen Sciences, Inc. In August of 2008, Dr Cox left Perlegen to join Pfizer's newly established Biotherapeutics and Bioinnovation Center.

Dr Cox is certified by both the American Board of Pediatrics and the American Board of Medical Genetics.

He has served on several international and national councils and commissions including the Council of the Human Genome Organization (HUGO) and the National Bioethics Advisory Commission (NBAC), He presently serves as a member of the Health Sciences Policy Board of the Institute of Medicine.

Dr Cox's honors include election to the Institute of Medicine of the National Academy of Sciences.

.....

New insights into the genetic basis of a large number of common human diseases have emerged in recent years through the application of genome-wide association studies (GWAS) employing common SNPs. However, the vast majority of the genetic loci identified to date account for a very small fraction each disease, requiring of thousands, if not tens of thousands, of affected

individuals in order to validate and replicate any particular genetic association. As a consequence, the GWAS approach has limited ability to address many important clinical outcomes, where only hundreds rather than thousands of affected individuals are available for study. When compared to common DNA variations, rare human DNA variants associated with human disease have been found to account for a significantly larger fraction of any particular disease. Recent technical advances in DNA sequencing technology, which provide a dramatic increase in sequencing throughput along with decreases in sequencing cost, now allow for the study of rare variants, enabling exploration of the genetic basis of a much broader range of clinically important outcomes than has been possible using the GWAS approach alone. By using DNA sequence analysis to identify genes with an altered frequency of rare variants in individuals with adverse clinical outcomes as compared to those with favourable clinical outcomes, studies employing hundreds, rather than thousands of individuals can identify robust genetic associations with a broad range clinically important questions. Situations in which a positive clinical outcome is associated with a significantly increased frequency of rare, DNA sequence variants resulting in loss of gene function are particularly informative. Such examples identify valuable targets for the generation of novel drugs, as well as providing valuable diagnostic tools for patient stratification.