Conference summary

Navigating the Sea of Genomic Data, October 28-29, 2015

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ABSTRACT

Background. The rapid pace of biomedical discoveries in the past few years has resulted in substantial advances in our ability to diagnose, treat, and prevent a wide variety of diseases. The sequencing of the human genome offered the possibility of understanding the etiology, pathogenesis, and risk of developing disease from a genetic perspective and has resulted, for example, in the development of genomic-based diagnostic or risk-assessment tests for a number of medical and dental conditions. To assess the scientific evidence underlying such tests and determine whether they may be useful in clinical practice, practitioners need to have a basic understanding of the state-of-the-science of genomics and genetic testing.

Objective. To assist practitioners in understanding the science of genomics, the American Dental Association and the Task Force on Design and Analysis in Oral Health Research co-sponsored a landmark conference, Navigating the Sea of Genomic Data, held October 28-29, 2015, at the American Dental Association headquarters building in Chicago, IL. The purpose of this conference was to review the basics of genomic science, promote sound design and analysis of genomic studies of oral diseases, and provide a basis or "framework" to guide practitioners in assessing new development in genomics and genetic tests for oral diseases.

Overview. Presentations at this conference were made by 9 world-renowned scientists who discussed a wide range of topics involving genomic science, genetic testing for rare mendelian single gene disorders, and genetic testing for assessing the risk of experiencing common complex diseases. This article summarizes the key points and concepts presented by the speakers.

Practical Implications. It is essential for oral health care professionals to have a fundamental understanding of genomic science so that they can evaluate new advances in this field and the use of genetic testing for the benefit of their patients.

Key Words. Genetic testing; genomics; oral disease.
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The rapid pace of biomedical discoveries has substantially enhanced our ability to diagnose, treat, and prevent a wide variety of diseases. As a result, practitioners are faced with the challenge of assessing the scientific evidence that supports the use of new technologies and, in the case of commercial products, the validity of marketing claims. Sequencing of the human genome[1] has made it possible to understand the etiology, pathogenesis, and risk of developing disease from a genetic perspective and has led to the development of genomic-based diagnostic and risk-assessment tests. To evaluate whether a genetic test may be useful in clinical practice, practitioners need to have a basic understanding of the state of genomic science, as well as its limitations.

To assist oral health care professionals in assessing the science of genomics, the American Dental Association and the Task Force on Design and Analysis in Oral Health Research[2,3] cosponsored a landmark conference, *Navigating the Sea of Genomic Data*, held October 28-29, 2015, at the American Dental Association headquarters building in Chicago, IL. The purpose of the conference was to review the basics of genomic science, promote sound design and analysis of genomic studies of oral diseases, and provide a basis or framework to guide practitioners in assessing new developments in genomics and genetic tests for oral diseases. This article summarizes key points and concepts presented by the speakers. Box 1 lists the speakers and the titles of their presentations.

FUNDAMENTAL DEFINITIONS AND CONCEPTS

Because much of the terminology used at the conference may be unfamiliar to some readers of The Journal of the American Dental Association, Box 2[4] provides a glossary of commonly used terms. The term *genomics* refers to the

BOX 1

Conference presentations.

Big Data, Genomics, and Reproducible Research (Keynote Speaker): John Ioannidis, MD, DSc, professor of health research and policy, Stanford University, Stanford, CA
Emerging Concepts in Understanding Genomics; Genetic Testing in Dentistry: Thomas Hart, DDS, PhD, director, Dr. Anthony Volpe Research Center, American Dental Association Foundation, Gaithersburg, MD
Lessons From GWAS Studies: Teri Manolio, MD, PhD, director, Division of Genomic Medicine, Research, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD
Predictive and Not: Understanding the Mixed Messages From Our DNA: A. Cecile J.W. Janssens, MA, MSc, PhD, professor, Faculty of Epidemiology, Emory University, Atlanta, GA
Statistical Issues in Data Analysis: John Barnard, PhD, head, Section of Statistical Genetics and Bioinformatics, The Cleveland Clinic, Cleveland, OH
Epigenetics, RNA, and Missing Heritability: Michael Stitzel, PhD, assistant professor, The Jackson Laboratory of Genomic Medicine, Farmington, CT
Future of Genomic and Genetic Testing in Healthcare: Robert Wildin, MD, chief, Genomic Healthcare Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD
Genomic Education for Clinicians: Debra Regier, MD, PhD, director of genetic and genomic education, Children's National Health System, Washington, DC
A Strategy for Genetic Testing of Mendelian Dental Defects: James P. Simmer, DDS, PhD, professor of biologic and material sciences, School of Dentistry, University of Michigan, Ann Arbor, MI

entire genetic makeup contained in the chromosomes of an organism (that is, the genome), and the term *genetics* refers to the effects that genes have on an organism. The genome encompasses all of the genetic material in an organism as expressed in its chromosomes' DNA. DNA consists of a double helix of repeated pairs of nucleotides or bases (adenine, thymine, guanine, and cytosine) (Figure 1).[5] Single-locus variants in the sequences of these four DNA base chemicals are called *single nucleotide polymorphisms* (SNPs). For example, a SNP is present when some people have a cytosine and others have a thymine nucleotide in its place at a specific site on a chromosome. SNPs occur randomly at approximately every 100 to 300 locations along the sequence of the 3 billion base pairs in human DNA. Of the 20 to 30 million SNPs that have been identified, most appear to have no effect on cellular function, but a relatively small number are associated with disease or response to a drug.

GENOMEWIDE ASSOCIATION STUDIES

The fundamental biological event in genetics is DNA recombination between chromosomes as a result of meiotic separation of genetic information passed through generations by means of sexual reproduction. The classic family-based study design involves use of genetic analysis to study families over a *few generations* and has been used for many years to investigate rare diseases or traits that are inherited as single-gene mendelian traits. However, family studies are less useful for studying complex common diseases in which multiple genes interact in combinations with one another and with the environment. For these diseases, genomewide association studies (GWASs) having larger samples of people are used to investigate DNA variants (SNPs) that have accumulated over *many generations*.

GWASs most often have a case-control design that statistically compares the frequency of each genetic variant (SNP) in a sample of people drawn from a population having a phenotype (disease or trait) of interest (cases) with the corresponding SNPs in a matched sample of unaffected people (controls). Investigators typically use GWASs to compare hundreds of thousands of SNPs across the entire genome between case and control participants. Conceptually, the statistical analysis of case-control GWASs is relatively simple, involving multiple χ^2 tests. However, because the statistical tests are repeated hundreds of thousands of times, the likelihood of rejecting the null hypothesis and accepting false-positive associations of some SNPs with the phenotype is high if a conventional criterion of statistical significance, such as $P < .05$ or $P < .01$, is used. Therefore, the level of statistical significance required in GWASs for each SNP's test is set at $P < 10^{-8}$. This stringent criterion for each test is used so that the likelihood of accepting any false-positive association in a particular GWAS will be no more than $P < .05$.

As in any valid case-control study, careful matching of case and control participants is essential, and it is important that the disease or trait (phenotype) is defined precisely and, for multicenter studies, standardized among enrollment sites. It also is critical that in a given study, the case and control participants have the same ethnic ancestry to avoid spurious associations that can result from the presence in different ethnic groups of SNPs that may be unrelated to the condition of interest. Before GWAS results can be accepted as applicable to the general population, they must be replicated in independent studies of populations having different ancestries.

Many GWASs must involve thousands of people to find statistically significant associations between diseases or traits and SNPs. Meta-analyses and consortia of investigators often are used to pool data and achieve these

ABBREVIATION KEY. **GWAS:** Genomewide association study. **SNP:** Single nucleotide polymorphism.