dentistry
in the age of genomics
The problem [with genetic research] is, we’re just starting down this path, feeling our way in the dark. We have a small lantern in the form of a gene, but the lantern doesn’t penetrate more than a couple of hundred feet. We don’t know whether we’re going to encounter chasms, rock walls or mountain ranges along the way. We don’t even know how long the path is.

— Francis S. Collins, MD, PhD
Former Director, National Human Genome Research Institute; Director, National Institutes of Health
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MESSAGE FROM THE HERMAN ROBERT FOX DEAN

Charles N. Bertolami, DDS, DMedSc

Herman Robert Fox Dean

With the achievement in 2003 of the completion of the sequencing of the roughly three billion letters of DNA that spell out the genetic code of our species, the field of genomics emerged as one of the most important areas in the biological sciences. Genomics—the study of all the genes within an organism and their interactions with one another as well as within the environment—has led to great advances in our understanding of the biological information contained in our own genome and in those of many other organisms. These advances, in turn, have opened an entirely new era in medicine and, not surprisingly, in dentistry.

In this issue of Global Health Nexus, we explore some of the ways in which genomics is influencing dental research and the implications of this research for patient care. We are privileged to begin this section with an article by Harold Slavkin of the University of Southern California (USC), who provides an in-depth introduction to the subject, along with personal reflections on the history of the human gene sequencing project and his predictions for the future of dentistry in the age of genomics.

We are also honored to include an interview with the distinguished scientist Bruce Paster of The Forsyth Institute and Harvard University, who is the leading authority on methods for the rapid identification and enumeration of oral microorganisms and their roles in oral and systemic diseases. Rounding out this section is a discussion among senior NYU College of Dentistry faculty who are utilizing genomics in their research. These faculty members speak frankly about the challenges of interpreting the flood of data that has emerged from the sequencing of the human genome and about the possibilities for creating new knowledge and improved patient care based on these data.

The level of scientific sophistication reflected in these articles permeates and elevates the education of students in ways that can only occur where there is a commitment to cutting-edge research. Students at dental schools with such a commitment get something more from their education, and they will almost certainly use this experience as they proceed into various private practice and institutional settings.

This issue of Global Health Nexus also features a program that is unique to NYUCD in utilizing the expertise of psychologists to study the relation between the level of verbal and physical aggression that occurs between parents and the extent to which oral health problems occur in their children. The program, described on p. 32, has great potential for creating new knowledge, strengthening a community, and expanding resources for change and improved public health.

In this issue you will also learn about research being conducted collaboratively by the NYU College of Dentistry and its College of Nursing that has found that dentists and dental hygienists could screen a staggering 20 million Americans for chronic physical illnesses. The level of scientific sophistication reflected in these articles permeates and elevates the education of students in ways that can only occur where there is a commitment to cutting-edge research. Students at dental schools with such a commitment get something more from their education, and they will almost certainly use this and institutional settings.

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The biological revolution dividends continue to arrive! They are being delivered from universities, government laboratories, foundations, hospitals, and clinics, and from a growing number of biotechnology industries. These dividends are international, not restricted by national boundary conditions. They impact our language, how we think, how we diagnose, how we plan and implement clinical procedures, how we consider therapeuticsthat are gene-based, and even how we design and fabricate biomaterials for cell, tissue, and organ regeneration. It’s been and remains thrilling for all of us!

My personal exposure to the biological revolution started in high school, when I first heard about Watson and Crick and their discovery of the structure and possible biological functions of deoxyribonucleic acid (DNA) from my chemistry teacher, Miss Nellie Rogers. That was 1953. Later, as I was completing my dental studies, Francis Crick proclaimed, “We are living in a biological revolution,” as he received the Nobel Prize in 1964 along with James Watson and Maurice Wilkins. I heard more about this ‘revolution’ from Marshall Urist as he shared with me his discovery of bone morphogenetic factor.
during my seven years of private practice; we both practiced one day a week in the same building, and Marshall [an orthopedic surgeon and clinical scholar] became a close friend and my patient.

My awareness grew during my postdoctoral education and training, though I never would have imagined that I would attend the Asilomar Conference held in Monterey, California, in 1975, when recombinant DNA guidelines were drafted. Imagine being present at the inception of the rules and procedures for the human gene for insulin to be inserted into the genome of a bacteria, yeast, plant, or animal, and that organism producing recombinant human insulin protein for the treatment of diabetes and other important human therapeutics (growth factors, hormones, antibodies, anti-microbial therapeutics, and a large array of other pharmaceuticals).

In fact, Robert Swanson and Herbert Boyer founded Genentech—the first biotech company in the United States—in 1976 in South San Francisco. At that time, they reported cloning the gene encoding EGR (epidermal growth factor receptor, HER1) used in studies of cancer and cancer therapy.

Across the Bay, Bill Rutter and his research team founded Chiron in Emeryville, California, and enabled many advances, including recombinant insulin, a number of gene-based diagnostic tests for blood elements, and the Hepatitis B vaccine. Today, the United States is the largest market and leading consumer of biotechnology products in the world, and now home of more than 1,300 firms involved in achieving the goals of the biological revolution. Of the 5.5 million scientists and engineers in the United States, approximately 1.3 million are involved in the biological sciences and related industries. Biotechnology-derived pharmaceuticals were valued at $67 billion in 2010.

After production of antibodies to detect the major protein found in enamel (amelogenin), and identification of the messenger RNAs (mRNAs) for amelogenin in the late 1970s, my laboratory, including Mal Sneed, Maggie Zeichner-David, and Alan Fincham, in collaboration with Savio Wu (then at Baylor), would, in 1983, be the first to clone the mouse gene for amelogenin, the major protein found in the bioercamic identified as enamel. Along the way, several postdoctoral fellows in our research group, Ed Lau and James Simmer (now at the University of Michigan), discovered that the amelogenin gene produces multiple and different mRNA transcripts by a process termed ‘alternative splicing,’ and thereby produces multiple translation products or protein isoforms of varying molecular weights that enlarge the proteome. Alternative splicing is a common mechanism for the generation of multiple isoforms. Many genes are alternatively spliced in tissue-specific, developmentally regulated, and hormone-responsive manners. The central dogma of years ago that “one gene produces one messenger RNA that produces one protein” is no longer true. The total number of possible proteins from the genome can far exceed the number of genes.

The unexpected has always dominated my career. By the late 1980s, we had identified and mapped the human amelogenin gene to both the X and Y chromosomes (AMELK and AMELY). This was an unexpected discovery—a variant of a functional gene encoded in two different chromosomes. Thereafter, several investigators used our discovery for sex determination by genetic typing of amelogenin gene- and chromosome-specific fragments. Amelogenin genes also had utility in forensics.

We explored the molecular explanation of X-linked amelogenesis imperfecta (AI) localized to Xp22.1-p22.3. We produced a recombinant amelogenin protein for studies of protein-protein interactions associated with the initiation and control of bionimerization. We asked, “How does amelogenin function with respect to the crystal formation and growth associated with enamel?” In short order, we learned from genomics studies that there are multiple modes of inheritance for AI. There are five responsible gene mutations for AI, including amelogenin, ameloblastin, enamelin, enamelysin, and the transcription factor distal-less homeobox 3 gene.

Independently, Mary MacDougall (at that time a graduate student working with Maggie Zeichner-David and me) isolated and characterized the major non-collagenous protein found in dentin. She cloned the gene and eventually mapped the gene to the chromosomal location responsible for dentinogenesis imperfecta (DI), chromosome 4q21. From genomic studies we learned that genetic mutations in osteopontin, bone sialoprotein, matrix extracellular phosphoglycoprotein, dentin matrix protein 1, and dentin sialophosphoprotein are associated with an array of dentin genetic diseases and disorders.

In the mid-1990s, I was invited by Don Chambers to celebrate the 40th anniversary of the discovery of DNA by James Watson and Francis Crick. The celebration was held in Chicago at the University of Illinois and included the work of Rosalind Franklin, Norman Simmons—a dentist who, as a postdoctoral fellow, prepared the DNA used by Franklin for her X-ray diffraction studies—and Maurice Wilkins.

I spoke of emerging opportunities in oral medicine to utilize the revolution’s fruits for applications to diagnostics, treatments, therapeutics, and biomaterials. At that time, I predicted the delivery of genetic therapeutics for oral fungal infections such as candidiasis, the production of oral mucosal lubricants for xerostomia, the oral delivery of systemic gene-based therapeutics, genetic approaches to the design and fabrication of dental tissues, the production of recombinant proteins such as bone morphogenetic proteins for tissue regeneration, the production of vaccines to manage human papilloma viral infections, and the utilization of gene-based diagnostics to identify craniofacial syndromes. It was further evident to me at that time, just over 17 years ago, that genomics would also include microbial genomics and viral, bacterial, and yeast microbes (“the Microbiome”). These applications have become reality.
The following February both teams published their work—roughly 95 percent completion of the human genome; Francis’s team published in *Nature*, and Venter’s team in *Science*. Then, in October 2004, the entire Human Genome was completed. Imagine, 100 percent completion by 2004—the 6.2 billion nucleotides or bases, annotated within 21,000 genes encoded within and mapped to specific locations in the 23 pairs of human chromosomes, were identified. We had entered “the Post-Genomic Era.” Essentially, a “parts list of life” was now available online or in hardcopy. It was thrilling!

**THE SHORT-TERM DIVIDENDS FROM THE HUMAN GENOME**

Francis Collins is now director of the entire NIH enterprise. In 2000, when Francis was serving as director of the Human Genome Project, he shared his predictions with NIH leadership as to where the biological revolution was going. According to Francis and his PowerPoint presentation of 2000, there will be six major themes delivered as dividends from the completion of the Human Genome:

- Predictive genetic tests will be available for a dozen conditions
- Interventions to reduce risk will be available for several of these disorders
- Many primary-care providers will begin to practice genetic medicine
- Pre-implantation genetic diagnosis will be widely available, and its limits will be fiercely debated
- A ban on genetic discrimination will be in place in the United States
- Access to genetic medicine will remain inequitable, especially in the developing world.

Importantly, all six of Francis’s predictions from the year 2000 have come true. It is also fair to assert that the promise of a biological revolution in human health remains very real. It is further valid that many of us overestimate the short-term impacts of new technologies and underestimate their long-term effects.

**THE BIOLOGICAL REVOLUTION CONTINUES**

I have repeatedly learned that science informs research and development, technology, and clinical practice. Sometimes translational research that ultimately yields a clinical trial or material requires one or two decades and many millions of dollars. For over a century, scientific discoveries have been translated into technology that enables diagnostics, treatments and procedures, therapies, and biomaterials that have revolutionized the oral health professions.

The discovery of chemicals to achieve anesthesia revolutionized surgery. The discovery of X-rays led to radiology and how we image hard and soft tissue structures. The discovery of antimicrobial therapeutics profoundly changed clinical outcomes associated with acute and chronic infectious diseases—viral, bacterial, and yeast infections. A number of discoveries through adhesive chemistry led to sealants, an array of composite resins, and

Many of us overestimate the short-term impacts of new technologies and underestimate their long-term effects.
the bonding of porcelain to enamel. The discovery of fluoride and fluoridated drinking water to reduce the prevalence of tooth decay has been extraordinary. The discoveries from the digital revolution have and will continue to enhance how we see, how we take impressions, and how we design and fabricate restorations for tooth replacement. Science remains the fuel for innovations, applications, and advances in clinical dentistry, medicine, pharmacy, and nursing.

**GENOMICS 101**

Following fertilization, the single cell nucleus contains the entire human genome, 21,000 functional genes and 19,000 non-expressed pseudogenes, packaged within 23 pairs of chromosomes. In addition, a few dozen genes are inherited directly from our mothers via their transmission of the mitochondrial organelles within their ova. The mitochondria contains DNA (deoxyribonucleic acid) called mtDNA. Genomics is the study of all of these genes and their interactions with one another as well as with the environment. These collective genes are encoded within the nuclear DNA and the mitochondrial DNA within cells and represent “the parts list of life.” Beyond the fertilized ovum, following a series of cell divisions, we eventually become mature adults consisting of ten trillion cells, each somatic cell containing the complete human genome. The length of DNA that encodes these genes within each somatic cell is approximately six feet. The DNA is formed from 6.2 billion nucleotides or bases (T, thymidine; A, adenosine; G, guanosine; and C, cytosine).

The language of genetics is the sequence and patterns created from A, T, G, and C. Each codon within DNA encodes for a specific amino acid (e.g., alanine, methionine, proline, arginine, tryptophan, etc.). The sequence of amino acids therefore provides the information and bioactivity of a specific protein (enzyme, co-factor, hormone, growth factor, a structural building block of bone or dentin, neurotransmitter, etc.). Only two percent of the entire length of DNA encodes the information for functional genes. The remaining DNA contains highly repetitive sequences that do not encode genetic information. The functional genes encoded within the nucleus as well as the mitochondria produce a total of 100,000 different proteins and this is called “the proteome.” Each functional gene has an anatomy that consists of a promoter region, an enhancer region, and a series of exons that contain the encoded information, and interspersed introns that do not contain informative base sequences. At the end of each gene is a stop codon (AAA). In summary, the DNA in our cells contains chains of A, C, T, and G. More than six billion of these chemical bases, strung together in 23 pairs of chromosomes, exist in every single somatic cell in our body. Along this enormous sequence of chemical bases, one in every 1,200 bases, on average, will differ. This difference is a source of genetic variance among people, known as single nucleotide polymorphisms or SNPs. From the investment in the Human Genome Project, we now have 10 million SNPs known to occur in the human genome and these have become “tools” for analyzing human genetic variance around the world now annotated and assembled in the International HapMap Project (see http://hapmap.ncbi.nlm.nih.gov/whatishapmap.html).

The investment in genomics has provided the mechanisms for tissue-specific, developmentally appropriate, and hormone-responsive gene regulation throughout the human lifespan. We are now on the verge of “the $1,000 genome” that can enable the detection of subtle variants, mutations, or misspellings that reveal human disease, disorders, resistance or susceptibility, and even a sense of our ancestral histories. High throughput genotyping, the availability of millions of SNPs, and bioinformatics have enabled “personalized medicine and dentistry.”

**INTRODUCING “-OMICS” IN THE POST-GENOMIC ERA**

How will we utilize the various “-omics” in the oral health professions? First, let’s untangle some of the emerging terminology. In the emerging lexicon of “-omics,” we identify:

- Genomics
- Epigenomics
- Transcriptomics
- Proteomics
- Metabolomics
- Diseasomics
- Pharmacogenomics
- Proteomics
- Metabolomics
- Genomics
- Transcriptomics
- Proteomics
- Metabolomics
- Diseasomics
- Pharmacogenomics
- Genomics
- Transcriptomics
- Proteomics
- Metabolomics
- Diseasomics
- Pharmacogenomics

In these examples, “-omics” is used to modify a term based upon large databases that enable alignment and integration of enormous amounts of information.

- Genomics describes the complete set of genes in organisms in terms of gene structure and function(s)
- Comparative genomics is the study of many diverse organisms—viral, bacterial, yeast, plant, and animal—for analyses in evolution, environmental studies, and/or health and disease.
- Epigenomics is the study of all of the chemical modifications (methylation, acetylation, etc.) beyond the inherited genetic information, that can modify or regulate many features of the human condition, such as metabolism.
- Transcriptomics describes the total number of messenger RNA transcripts derived from genes. As humans contain 21,000 different functional genes in the nucleus of every somatic cell in the body, the number of transcripts (the transcriptomes) is far greater, likely exceeding 100,000 different mRNAs.
- Metabolomics describes all the genes associated with metabolism, metabolism of nutrients as well as drugs. Genes encoded within chromosomes in the nucleus of every somatic cell in our body, as well as genes encoded within the mitochondrial DNA in the mitochondria directly inherited from our mothers, cooperate to regulate metabolism.
- Diseasomics describes diseases and their relationship to genes, micro- and macro-environments, and social determinants. This field of inquiry incorporates a taxonomy of networks that has the potential to unify various forms of databases. Biomedical researchers are attempting to redefine diseases by clustering or finding patterns and associations between different symptoms, ages, physiology, socioeconomic determinants, genes, protein, and so much more. The various databases suggest that diseases often cluster within specific socioeconomic groups that further align with a number of risk factors associated with disease and disorder patterns. For example, Genomics is the study of all genes [within an another as well as with the environment. nuclear DNA and the mitochondrial DNA organism] and their interactions with one These collective genes are encoded within the within cells and represent ‘the parts list of life.’
analyses between children, poverty, diabetes, obesity, hypoglycemia, and hyper-insulin databases are starting to change nosology or the classification of disease.

Pharmacogenomics describes all genes that affect or are affected by pharmaceuticals such as non-steroid anti-inflammatory drugs, analgesics, and psychotropic drugs. These areas of exploration, and the plethora of data sets reflecting the yield from the biological revolution of the last 60 years, clearly impact diagnostics, therapeutics, biomaterials, and clinical outcomes throughout the health professions, including the oral health professions. I’m imagining that the dividends from these quarters will significantly impact how we understand and manage autoimmune disorders, chronic facial pain, and xerostomia.

PERSONAL REFLECTIONS REGARDING THE BIOLOGICAL REVOLUTION
There is a nexus formed by the convergence of clinical medicine, clinical dentistry, and the biological revolution. The dividends from the discovery of DNA, recombinant DNA technology, and the emerging field identified by “-omics,” continue to change the human condition and how we advance as health professions.

Fundamental scientific discoveries were augmented by clinical observations that elucidated the inheritance of single-gene, or monogenic disorders, also known as Mendelian disorders since they are transmitted in a manner consonant with Mendel’s laws of inheritance. Today, the National Library of Medicine at the NIH in Bethesda, Maryland, hosts the online compendium known as Mendelian Inheritance in Man (OMIM) that has annotated more than 100 years of documented human genetic disorders. We now have many thousands of disorders and these can be readily accessed on the Internet or in hardcopy. Rapid advances reveal that 20 percent of human diseases are now known to be inherited as Mendelian single gene mutations, whereas 80 percent are complex and reflect multiple gene and multiple environmental interactions.

As we look to our futures, the future of the oral health professions, I suggest we ask ourselves a simple question: “Are we ready for the dividends from the biological revolution?” Are we allocating resources to educate and train oral professionals for the future, a future that offers the promise of gene therapies, increased cell, tissue, and organ regeneration, integration between digital and biological ways of knowing, and so much more? Are we prepared to utilize biology and gene-based therapeutics in the diagnosis and treatment of oral diseases and disorders? Are we ready to employ saliva as an informative fluid from which we can diagnose diseases and monitor the efficacy of treatments? Are we prepared to employ growth factors and other biological ingredients in the repair and regeneration of craniofacial, oral, and dental tissues? Are we prepared to use the principles and data gained from the $1,000 genome, from personalized medicine, in the oral health professions? Are we ready?

A list of references appears in the online version of this article at http://www.nyu.edu/dental/nexus/index.html.
Gene-based Discoveries May Help Clinical Wishes Come True: A CONVERSATION WITH DR. BRUCE PASTER

Bruce J. Paster, PhD, is senior member of the staff and head of the Department of Molecular Genetics at The Forsyth Institute, and professor of oral biology medicine, infection and immunity and director of the Human Microbe Identification Microarray Core at the Harvard School of Dental Medicine. The major research objective of the Paster laboratory is to develop methods for the rapid identification and enumeration of oral microorganisms so that we may elucidate their roles in oral and systemic diseases. The Paster laboratory utilizes a number of molecular techniques, such as nucleic acid sequencing, gene amplification via polymerase chain reaction, gene cloning, DNA probe development, DNA hybridization, in situ hybridization, and, more recently, DNA microarrays. In a recent conversation with Global Health Nexus, Dr. Paster addressed the promise and challenges inherent in genomics research.

Global Health Nexus (GHN): How does human genome sequencing impact microbiology?
Dr. Paster: It lets us understand genes that affect the interaction of bacteria with our bodies. Almost more important is the sequencing of the genomes of human-associated bacteria, known as the microbiome. Information from these studies is allowing us to better understand how our microbiome helps us digest our food, how bacteria may cause disease, and, better yet, how bacteria keep us healthy.

GHN: What is Forsyth’s role, and your role in particular, in the Human Microbiome Project (HMP) funded by NIH?
Dr. Paster: Forsyth scientists are the major supplier of DNA from oral bacteria to the HMP genome sequencing centers. Forsyth has DNA for production of approximately 200 reference genomes. My role has focused on analysis of a particular subfraction of ribosomal RNA known as 16S rRNA to better understand the microbial diversity of the oral cavity.

GHN: Many studies focus on a specific group of bacteria associated with oral diseases. How important is it to study genomics in the oral cavity in the effort to improve oral health?
Dr. Paster: It is extremely important to study the genomes of the oral bacteria because we can discover genes involved in disease processes, such as antibiotic resistance genes and toxins. With the availability of the genome sequences of most of the cultivable oral species, data mining will likely reveal much information.

GHN: What are the questions and the challenges involved in doing genomics in the oral cavity?
Dr. Paster: Questions include the following:
- What bacteria are present in the oral cavity?
- How stable is the oral microbiome over time?
- What proteins, enzymes, toxins, etc., does each specific bacterium make?
- Can genetic factors be identified that control host-bacterial interactions?
- What is the role of oral bacteria in human health and disease?

Among the challenges are understanding:
- which of the over 700 common species in the oral cavity are important in health and disease,
- how the significant variability in the oral microbiome from person to person affects our analyses,
- how diet and the person’s health status may affect the oral microbiome,
- the complexity of bacterial-host interactions.

GHN: What is the HOMIM project and what is its current status?

It is extremely important to study the discover genes involved in disease processes, With the availability of the genome data mining will likely reveal much genomes of the oral bacteria because we can such as antibiotic resistance genes and toxins. sequences of most of the cultivable oral species, information.”
Dr. Paster: Since 1986, Dr. Floyd Dewhirst, who is also at The Forsyth Institute, and I have used molecular analyses based on 16S rRNA sequencing to identify over 700 predominant bacterial species in the oral cavity. About 35 percent of these species has not yet been cultivated. Using this information, we developed for our own research the Human Oral Microbe Identification Microarray, known as HOMIM, which allows for the simultaneous detection of about 300 of the most prevalent oral bacterial species, including many that have not yet been cultivated.

Since 2008, HOMIM (http://mim.forsyth.org) has also been available to the scientific community for the rapid determination of bacterial profiles of clinical samples from the human oral cavity, esophagus, and lung. HOMIM is recognized worldwide as a valuable research tool by many investigators from academic institutions (over 60 teams), government (six teams), and industry (10 companies). Twelve peer-reviewed publications, three reviews describing HOMIM, and many presentations at national and international meetings have resulted from these studies. Under development are microarrays that target bacterial species from the human gastrointestinal tract and the macaque oral cavity.

GHN: What is the relevance of the HOMIM project for oral research?

Dr. Paster: The HOMIM project has tremendous relevance for oral research in the following areas:
- determining and comparing bacterial associations in oral health and disease, including different types of periodontitis, caries, gingivitis, ventilator-associated pneumonia, endodontic and odontogenic lesions, abscesses, and halitosis,
- determining the efficacy of therapies, e.g., mouth rinses, antibiotic treatment, scaling and root planing, and laser or periodontal surgery,
- determining the progression of oral diseases,
- determining those patients at risk for periodontitis and other oral diseases.

For my own research, I am using HOMIM to identify those microbial species or microbial profiles (“danger profiles”) of periodontal sites at risk for developing periodontal disease.

GHN: What have you discovered involving microbial genomics in the oral cavity that has relevance for systemic diseases?

Dr. Paster: HOMIM indeed has utility beyond determining bacterial associations in oral health and oral diseases. Specific oral bacterial species, bacterial complexes, or entire oral microbial profiles, as determined from HOMIM analyses, may serve as potential biomarkers for non-oral systemic diseases. In a recent publication, we noted a significant decrease in overall diversity in the oral microbiome of pediatric Crohn’s disease as compared to that of healthy children and children with ulcerative colitis.

In another study, we reported that there may be oral microbial biomarkers for pancreatic cancer. For example, Neisseria elongata and Streptococcus mitis were detected significantly less often in the saliva of cancer patients than in saliva of healthy controls. In contrast, levels of Granulicatella adiacens were significantly higher in cancer subjects.

GHN: Will these findings lead to changes in the way dentistry is practiced, with specific reference to pathogen-based early detection, which will allow instantaneous chairside quantification of oral bacteria in plaque or saliva samples?

Dr. Paster: If microbial danger profiles can be used to identify specific sites at risk for periodontal disease, clinicians will be able to focus on those sites for therapy, such as scaling and root planning and localized antibiotic delivery. Progress can be determined after treatment by monitoring the response of the “at-risk” microbial profiles; e.g., change to microbial profiles typically detected in healthy sites. Consequently, we may be able to halt disease before it occurs.

For example, with systemic diseases, such as pediatric Crohn’s disease, the presence of certain bacterial species or bacterial complexes in the oral cavity would be indicative of those children who have not yet been diagnosed with the disease. If successful, the impact is huge for Crohn’s patients since early diagnosis means prompt and proper treatment, not only for those with Crohn’s but for those with other intestinal diseases or disorders. The key here is that this would be a non-invasive diagnostic test—patients would much rather spit in a tube than provide a stool sample, or even be subject to a biopsy.

GHN: Despite global efforts toward prevention and cure of infectious diseases, they remain major problems. What are the implications for using molecular genetic approaches to study various aspects of infectious diseases with respect to prevention and cure?

Dr. Paster: Bacterial identification based on 16S rRNA sequences is much more accurate and rapid at identifying bacterial species than the older phenotypic methods that relied on culture techniques. The molecular methods can also be used to identify microorganisms that cannot presently be cultivated, which represent at least half of all human-associated bacterial species. Who is to say that those species that you cannot grow are any less important than those you can grow?
Dentistry in the Age of Genomics: Q&A with NYUCD Researchers

A group of senior researchers at the NYU College of Dentistry is actively engaged in exploring genomics as a means of advancing knowledge of human genetics, the origins and evolution of human diseases, and the development of therapeutic initiatives to treat disease.

Global Health Nexus recently asked several of these individuals to talk about the future of genomics in dentistry, including individual research projects utilizing genomics. Participants included Dr. Louis Terracio, professor of basic science and craniofacial biology and vice dean for research; Dr. Daniel Malamud, professor of basic science and craniofacial biology and director of the HIV/AIDS Research Program; Dr. Brian Schmidt, professor of oral and maxillofacial surgery and director of the Bluestone Center for Clinical Research; Dr. Walter Bretz, associate professor of cariology and comprehensive care; Dr. Steven Engebretson, associate professor and chair of the Ashman Department of Periodontology and Implant Dentistry; Dr. Page Caufield, professor of cariology and comprehensive care; and Dr. Yihong Li, professor of basic science and craniofacial biology.

Global Health Nexus (GHN): Dr. Terracio, as vice dean for research, could you provide an overview of the prospects for dental research and patient care in the age of genomics?

Dr. Terracio: Genomics is only one of many 'omics that are populating modern science. Proteomics—the large-scale study of proteins—is the other big area that people are looking at. People are using many other forms of evaluation for data collection and any of those that are dominating the research front in medicine are appropriate to dentistry. The head/neck/oral cavity lends itself to all the same sorts of evaluations that one is seeing dominating medicine. So there’s no reason why dentistry would do anything but be a major player in genomics research, depending on the disease.

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Vice Dean Louis Terracio

There are folks in this group who are interested in cancer, like Brian, and those who are interested in genomic analysis, like Walter, Yihong, and Page, who are all interested in the microbiome, or the totality of microbes, including their genetic elements and environmental interactions in a defined environment. Dan is involved in multiple investigations using saliva samples collected with a swab from the mouth as a less-invasive and instantaneous alternative to drawing blood and sending samples to the laboratory to determine risk for and onset of disease. Steve is doing research with the ultimate aim of treating diabetes. Page and Yihong are using genetic criteria to conduct research in caries development. It’s where we should be.

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Many people are thinking about using genomics as a tool for studying dental diseases. [But] if a researcher focuses exclusively on oral diseases, there are a smaller number of opportunities compared to systemic diseases.

GHN: What role does genomics play in the research that each of you is conducting?

Dr. Malamud: In discussing genomics in dentistry, I think that you can look at this in two ways. First, the oral cavity is a source of DNA that allows you to look for anything in the entire body, and if you do a Pub Med search correctly, you find that 90 percent of the publications refer to the oral cavity as the easiest way to obtain DNA. Second, many people are thinking about using genomics as a tool for studying dental diseases. To Lou’s comment about less money available for genomics technology at dental schools as opposed to medical schools, I would add that if a researcher focuses exclusively on oral diseases, there are a smaller number of opportunities compared to systemic diseases. Since there are a limited number of dental diseases, it’s not surprising that there is less research in this area.
A key opportunity for dentistry in genomic research lies in being able to predict a person's risk for developing dental caries...This approach is applicable not only to the development of dental diseases, but also to systemic diseases. 

Dr. Walter Bretz

Potential genetic and environmental risk factors play an important role in the research that my collaborators and I conduct to understand the etiology of early childhood caries (ECC). 

Dr. Page Caufield

RA patients and patients with chronic RA.

Dr. Caufield: Potential genetic and environmental risk factors play an important role in the research that my collaborators and I conduct to understand the etiology of early childhood caries (ECC), one of the major public health problems affecting millions of preschool children, especially those in low-income populations both in the United States and around the world. Using such approaches, we were able to characterize a number of risk factors associated with cariogenic bacterial colonization in children with ECC. In a newly funded NIH project, we will look further at the genetic determinants associated with the development of ECC.

Dr. Li: The question of whether or not there is a significant difference in the microbial species between healthy and diseased conditions...We are trying to understand the interaction of oral microbial diversity with other diseases, including HIV infection, oral cancer, gastric precancerous lesions, and infants of preterm/low birth-weight. Other key questions are whether or not changes in the relative abundance of members of the microbial communities are clinically important, and how oral microbes interact with host and immune environmental factors.

Dr. Schmidt: I've always been interested in the incidence and prevalence of oral disease. So compare periodontal disease to heart disease. Probably very similar prevalence, but we do much more in terms of cardiovascular disease. Let's take head and neck cancer as an example. There will be 50,000 cases of head and neck cancer in the US this year.

Dr. Brian Schmidt

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Dr. Yihong Li

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Dr. Yihong Li
There will be 10,000 brain cancers. The genome project has given us much more information and we’ve been able to glean clinically useful information for brain cancer, whereas for oral cancer we’ve not been able to do that, so it’s a much more complex challenge.

Oral cancer has what we’ve termed “capricious clinical behavior.” Patient A will have an oral cancer, it can be big and that patient will get treatment and will be alive in five years. Patient B has a much smaller oral cancer. They look exactly the same under the microscope, and that patient doesn’t live for two years. If you’re diagnosed today with oral cancer, you have a 50 percent chance of being alive in five years, and we don’t know which side of that 50 you’ll be on. That’s been the real challenge.

Just because we understand the genomics, that doesn’t mean it’s a blueprint for how that cancer’s going to behave. So for the last eight to nine years we’ve been trying to identify a genomic marker that will help us understand which patients will get metastasis and then the cancers are so good at DNA mutation that they evolve, so cancers recapitulate evolution in nature, and these cancers evolve so the metastasis at a genomic level looks totally different from the oral cavity primary tumor, which just adds another layer of complexity. Within the last year we have developed what’s called “massively parallel genome sequencing,” which means that you can sequence the entire genome (the parts of the gene that code information for protein synthesis) for very complex genes up to 50 exons in a single gene.

**Dr. Engebretson:** One of the things we’re looking at in the area of periodontal disease is gene expression research using microarray technology, and it’s giving us the opportunity to study thousands of genes from a single tissue sample. Even though costs are still high, prices have come down enough to allow us to look at biomarkers in gene expression profiles for patients who have responded well to therapy and for those who have responded less well. As in cancer research, we might someday be able to use a gene expression profile to help with a prognosis for a disease.

The interdisciplinarity nature of this type of research is really strong, particularly with regard to bioinformatics, which requires expertise in a number of different disciplines to get any useful information. A lot of different types of problem-solving skills go into this type of research.

Let me give you an example of a program using bioinformatics that we’ve been using for gene expression profiles. It was developed, I understand, by members of the KGB who defected to the West and somehow wound up in Bethesda, Maryland, where they were put in charge of a project called natural language programming. These people had experience writing algorithms that go out into cyberspace and pick up associations or words that are close together and other words that are far apart in order to interpret information about the ways the spites were passing messages. They decided to look at biology in the same way, using the same process to create software to find associations between molecules or genes and then map them out to see how they interact.

You can always tell how two things interact, but what about the things around them? This program allows you to see what the surrounding interactions are and what their significance is. These biological association networks can then help to identify biological pathways that are relevant to disease study and allow for experimentation to go forward. These programs know nothing about periodontitis or inflammation and they don’t care, but they know how to write programs that can help me to find out this information.

**GHN:** What do you see as the role of genomics in dental education and practice?

**Dr. Terracio:** A key reason for genomics education for dental health professions is that education is about the future, not the past, and we have entered an era in which genetics and genomics are playing a vital role in oral health research and dental practice. Each new day brings advances in genomics that add to the number of dental conditions whose genetic component is understood. The need for dental professionals to understand, recognize, and utilize genetics and genomics in their daily practice grows commensurately with these scientific advances.

Dentists have long recognized a genetic component to dental health problems, especially in the areas of abnormal tooth formation or physical malformations, such as a cleft lip or palate, resulting from hereditary conditions. But patients now expect more, whether it’s their risk for periodontal disease, or the connections between oral and systemic diseases, or the value of utilizing genetic tests to predict risk of disease in individual patients. Our students need to review the scientific literature and be able to evaluate it.

From the standpoint of what the practitioner needs to know, while it might not be imperative to learn to do informatics, practitioners should know how to assess the literature, because biomarkers for oral cancer and periodontics and other oral diseases may turn out to be valid, and practitioners need to know how they can best advise their patients about whether or not they should have this analysis.

**Dr. Bretz:** We had a large sample of twins and applied whitening procedures to them. Although both groups responded well to the whitening procedures, the identical twins had much less variation in the treatment response than the fraternal twins, suggesting that there might be a genetic component operating. Anecdotally, if you read the literature, many studies have found that some people respond very fast to whitening procedures, whereas others do not. So I think that practitioners will eventually find those kinds of applications especially useful.

**Dr. Engebretson:** A related area that may turn out to have special interest for the practitioner is pharmacogenetics, the branch of pharmacology that deals with the influence of genetics on a person’s response to specific drugs, and with tailoring a drug therapy at a dosage that is most appropriate for an individual patient.

**Dr. Schmidt:** The reality is that it is difficult to fit all the new information—on genetics and biochemistry and genetics and immunology and pathophysiology and genetics and bioinformatics—into a four-year dental school curriculum and into a dental practitioner’s continuing education. But that shouldn’t stop us from seeking ways to disseminate this information. We need a biomarker for insatiable curiosity.

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**Dr. Louis Terracio**