Transfer of Advances in Science into Dental Education

Genetics in Dental Practice: Social and Ethical Issues Surrounding Genetic Testing

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Abstract: It is evident that human genetic variation is associated with many if not all human diseases including the more prevalent chronic diseases. As a result, genetics is becoming integrated into health care in all medical specialties, including oral medicine and its specialties. At the level of public health, genetic information will become increasingly important in research, policy, and program development. As application of genome technologies moves from the research laboratory to the clinical setting, a complex array of challenges will face dental clinicians in their efforts to use genetic information to improve health care and prevent disease on an individual, family, and community level. The broader social, ethical, and legal implications raised by the clinical use of genomic information have not received the same attention as did recent gene identification aspects of the Human Genome Project. The goal of this review is to foster attention and dialogue within the dental community of the ethical and social issues emerging from the availability of genetic information. Specific areas addressed include genetic testing, confidentiality, discrimination, informed consent, risk communication, and professional education.

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Sequencing and annotation of the human genome is scheduled to be completed in 2003 to mark the fiftieth year anniversary of Watson and Crick’s report describing the structure of DNA.1,2 The Human Genome Project (HGP) began in 1989 and was envisioned to be a fifteen-year, $3 billion adventure to determine the sequence and location of each human gene.3 While the successful completion of the HGP’s primary goals represent significant scientific and technological achievements, the clinical and social impact of this project will become apparent over the coming years.4,7 The abundance of genetic information concerning our biological makeup provides critical insight into the quest to obtain a biological explanation of health, disease, and wellness at the cellular level. The rapid pace of discovery that characterized the HGP has fueled expectations that genetic information can be quickly integrated into clinical care paradigms. As attention shifts from gene discovery in research laboratories to the clinical utilization of genetic information, the impact of genomics on the diagnosis and treatment of human diseases is being considered, and the broader social, ethical, and legal implications of the HGP are now receiving increasing attention.8 The goal of this review is to foster awareness within the dental community of the ethical and social issues emerging from the availability of genetic information. This article will focus on the implications and applications of genetic information for genetic testing in oral medicine, because genetic testing is an area that has the potential to broadly impact delivery of oral health care in the near future.

All health care providers including dental clinicians will face challenges as genetic information and technologies are integrated into health care paradigms. The complex ethical, legal, social, familial, and professional aspects of these developments pose dilemmas that are often not addressed in professional education and training. From the initial conceptualization of the HGP, it was understood that the success of the project would carry broad ethical, legal, and social implications.3 A unique aspect of the project was that 5 percent of the original budget was set aside for research regarding the ethical, legal, and social implications of the project.9 The wisdom of this allocation cannot be overemphasized. Established in 1990, the Ethical, Legal and Social
Implications (ELSI) Research Program currently is the largest federal supporter of bioethics research. While the scope of ELSI is large, we will limit our discussion to the most common ethical and professional challenges posed by the HGP: confidentiality, discrimination, informed consent, risk communication, and professional education.

One of the fascinating characteristics of the HGP is the phenomenal pace of scientific discovery and the pressures to apply newly emergent genetic information to clinical care. As a result, efforts to incorporate genetic information into the clinical setting can outpace existing regulatory and educational environments. Whereas technological advances do not necessarily generate new ethical concerns, the advances can draw attention to how social, political, and economic factors influence the integration, use, and regulation of scientific advances. While great attention has been focused on broadly defined applications of genetic medicine for health care, the social implication of these developments has been less frequently reported. With the potential for revolutionizing health care comes the potential for inappropriate and even harmful implementation of care.10 Important issues must be appreciated and resolved to ensure that the promise of genetic medicine is not offered to society in a disproportionate or discriminatory manner. Dental clinicians need to be able to recognize a patient who is appropriate for genetic services, be aware of services available, assess risk, educate that patient and in some cases families, inform the patient and family, interpret genetic test results, and be aware of the ethical and professional challenges of genetic issues.

Ethical, Legal, and Social Issues (ELSI)

The planners of the U.S. Human Genome Project recognized that the information gained from mapping and sequencing the human genome would have profound implications for individuals, families, and society. While this information would have the potential to dramatically improve human health, they realized that it would also raise a number of complex ethical, legal, and social issues. How should this new genetic information be interpreted and used? Who should have access to it? How can people be protected from the harm that might result from its improper disclosure or use?

The rapid pace of genetic discovery and the pressures to clinically apply this genetic information and technology have created a dilemma for care providers who have generally had little formal genetics training. Dental clinicians are not alone in this lack of preparation, and it is important that they are aware of the valuable work that already exists and that can provide a foundation from which to begin consideration of ELSI-related issues.11-16 While aspects of some issues are unique to the dental profession, issues of access to care, privacy, and discrimination as well as the validity and utility of genetic testing information are shared by many areas of health care. Nonetheless, a framework for the integration of genetic testing into dental practice may be derived from policies, regulations, and consensus statements regarding genetic testing.12,17,21

Legal

Dentists, similar to other professionals subject to legal regulation, often have an overly simplistic view of the legal system. Pressures from multiple groups that represent diverse financial, patient advocacy, commercial, and health care interests to integrate genetics into medical care are challenging traditional medical paradigms.10-22 In many instances, genetic testing creates situations where there is little precedent and no appropriate gold standard to compare results. Interpretation of test results is not clear in some cases, and there is little and in some cases no guidance from knowledgeable, unbiased experts.13 Technologically, it is now possible to accurately and reliably test for genetic variance in individuals. As new scientific research implicates an ever-increasing array of genetic polymorphisms with disease susceptibility, there is a growing pressure to test for these genetic variants in clinical settings. Often regulatory bodies are not prepared to govern important aspects of genetic testing. Currently most governance relates to analytical validity. However, responsible governance relating to extremely important aspects of clinical validity, clinical utility, and informed consent is effectively lacking.

For many scenarios, it is difficult to know when to use a given genetic test, how to interpret results, and how to fully and appropriately provide information for informed consent. Additionally, because of unique aspects of genetic testing, supplementary issues of privacy must be considered. These can be difficult issues, made all the more daunting because of the limited genetics training received by many oral care providers.11,20,23-25
Genetic diseases present questions on the cutting edge of the law, and there is likely to be considerable uncertainty on many important legal points. Legal uncertainty is often a reflection of social or scientific uncertainty. Clear answers emerge less from the words of lawyers and judges than from the actions of professionals themselves, who ultimately set the standard of care. In any area of legal uncertainty, the dentist is best advised to adhere to the best scientific and clinical information available and to meet the ethical standards of the profession. To understand the available scientific information, a fundamental knowledge of genetic principles and concepts will be needed. While resolution of these issues will take time and input from multiple sources, it will be important for appropriate professional organizations to evaluate all available evidence and to render opinions to help guide clinical care decisions.

Confidentiality

Confidentiality issues that initially seem routine components of practice take on added dimensions when applied to genetic testing. Genetic information can be intensely private, and generalization of this knowledge can have implications for a patient’s extended family as well as his or her employment and access to health care. While policy can be developed at the state and federal level, privacy issues must be integrated into clinical practice scenarios. Legislators to date have said little about how and when tests for mutations that predispose individuals to develop diseases should be incorporated into clinical and public health practice. Most concern relates to how information about genetic risk factors will be used to interfere with an individual’s access to employment and health insurance. As it becomes increasingly possible to identify individuals who are at increased risk for certain diseases, we must guard against potential cases of job discrimination, preventing individuals from the right to work as well as effectively denying access to aspects of health care. Although privacy debates are driven primarily by fear of unfair and discriminatory consequences, there is also motivation to ensure privacy so that individuals are not deterred from having beneficial tests and engaging in health-promoting behaviors.

Genetic information is not fundamentally different from other health information except that genes cannot typically be changed, and hence can impart a deterministic aspect of health. Genes can tell us about health risk factors, but so can other factors such as lifestyle, environment, and diet. Approximately forty states have laws that treat genetic information separately from other health information. Laws were felt necessary due to concerns about stigmatization and discrimination by both employers and insurers. The laws try to address the issue that the treatment unit is a family rather than an individual, but again other types of health information also have significant implications for family members. Issues of information privacy become complicated in the increasingly informatic age. Genetic information should be protected with the same vigilance as other medical information.

Although dentists treat individuals, implications of genetic testing are not always limited to the individual. Genetic test results for one person may reveal genetic susceptibilities in the parents, siblings, and children of the patient. Therefore, sharing genetic information about one person can inadvertently disclose risk information about another family member. Dentists caring for families will be faced with the situation in which one family member may desire genetic testing while other family members either do not want testing or are unaware of hereditary risks. The American Society of Human Genetics published a position statement in 1998 addressing this issue and concluded that maintaining confidentiality within and among families was an essential principle and that any breach of confidentiality can only be justified if a major harm would result from withholding information from a family member. In rare cases, a practitioner may have a duty to warn individuals who are at risk for hereditary conditions.

Discrimination

The potential for disclosure of genetic test results to third parties such as health, life, and disability insurance companies is an important concern that must be addressed. Cases of genetic discrimination are not currently common, but do occur. In addition to insurability issues, employers, the military, and educational systems such as schools may also use genetic test results to discriminate. Family conflicts or loss of insurance can be avoided by notifying patients about the potential impact of genetic testing information on other family members in advance of testing or referring the patient to a genetic counselor to assist the patient with creating a strategy to deal with these implications.
Informed Consent

To date, relatively few genetic tests have been ordered by dental clinicians, and consequently the dental community may not be aware of important aspects of informed consent related to genetic testing. Informed consent implies the clinician has thoroughly informed the patient about the potential benefits and risks of genetic information gathering and testing. Informed consent for genetic testing differs in at least a couple of ways from other types of medical testing and from informed consent for invasive surgical procedures. First, test results can have implications for other family members. Genetic information affects many family members in differing personal ways and sometimes carries psychological burdens and the potential of genetic discriminations. The informed consent process must address the central issue that genetic information may affect many family members. The process should include taking a complete family history, a discussion of potential implications of testing on the patient and other family members, and an awareness of coercion within families or from practitioners to influence the decision to be tested.

Second, how one informs individuals of genetic test results is an important part of the informed consent process. Genetic testing results must be presented to patients in a confidential manner that enables them to understand the meaning of test results. As health care becomes increasingly personalized, it will be important that patients understand genetic tests so that they can participate in making complex decisions about their own care. Cultural sensitivities must also be considered. Genetic susceptibility testing can involve complex genetic issues and may raise unique concerns. Certain genetic alleles may be associated with more than one disease. Genetic variants of certain genes, e.g., pro-inflammatory cytokines such as IL-1 and TNFalpha, have been associated with multiple different diseases. For instance, IL-1 alpha polymorphisms have been associated with Alzheimer’s disease, cardiovascular disease, chronic periodontitis, and knee osteoarthritis. In such situations, aspects of informed consent can become complicated. What are the ramifications of testing for one genetic disease association if other disease associations are also reported? What are the ramifications of testing for one disease association if other disease associations are subsequently reported? Who will be responsible for explaining this information to the patient?

Risk Communication

Dentists are trained to communicate health risks to patients. However, risk communication for genetic testing is often a communication process involving uncertainty. Uncertainty about the appropriate use and accuracy of a genetic test is a common factor that compromises the ability of the practitioner to provide accurate information on the value of genetic tests for a specific patient. It is important that the practitioner knows the accuracy of test results and their appropriateness for a particular patient. The clinical validity of the test and its clinical utility must be known for accurate interpretation of test results. Testing in families with known mutations of specific genes is often fairly clear-cut. However, testing of individuals in families where there is no known mutation in affected family members is quite complex. The absence of a mutation does not necessarily mean the person has reduced risk of disease; rather he or she may have a mutation that simply has not yet been identified in the family. In addition, negative test results do not mean a zero risk for development of a disease but rather infer the person is now at the population risk for developing disease rather than being at increased risk compared to the general population.

Genetic information is probabilistic and has limits as well as benefits. Uncertainties about the accuracy or value of a given test make it difficult for practitioners to base decisions relating to a specific patient on uniform principles that apply to all cases. This is particularly true for emerging tests for genetic susceptibility to chronic diseases. The communication of uncertainty is perhaps the most difficult ethical and professional challenge faced by practitioners. The practitioner has the responsibility to introduce the concept of uncertainty or complexity into a patient’s perceptions. This is a difficult task in which the informed practitioner’s goal is to guide the patient to the best understanding possible about the accuracy, utility, and predictive value of the genetic test as well as to help the patient understand the relationship between having a specific gene allele and developing disease.

The risk-benefit determination for many genetic tests is not straightforward. Dentists will have to explore the factors of decision making with each client considering a genetic test. One practical tip is that the decision-making factors for one family are not transferable to the next because each client has a different perception of disease burden. In addition,
experiences with the disease in question or experiences with previous medical interventions vary from person to person. The informed consent process will need to indicate in clear terms the benefits and limitations of testing.

The emotional and psychosocial benefits and risks must next be considered. Empirical data are usually difficult to obtain, and published reports on patient experiences with testing are seldom available. The most common psychosocial benefits of testing that are likely to occur in dentistry include resolution of uncertainty and prognostic planning for a confirmed diagnosis. However, as susceptibility testing for genetic markers associated with complex disease states becomes available, difficulties in determining the meaning of test results on an individual level may prove emotionally and psychologically stressful, particularly if test results are not communicated appropriately. Psychological risks of genetic testing include stigmatization, insurance discrimination, the impact on family relationships, and adverse adjustments to diagnostic information among those testing negative or depression for those testing positive.

Professional and Continuing Education

The effective integration of genomic medicine into health care will require a transformation in genetics education and a general development of genetic literacy among providers and consumers. A real problem in the current health care environment is that most clinicians and support personnel have not been adequately prepared to facilitate the integration of genetic information to clinical care. This is entirely understandable, and in large part reflects the rapid emergence of medical genetics and its transition from a largely academic pursuit to a dynamic and practical part of health care. The rapid emergence of genetic medicine is likely to continue in the future, particularly given its potential to dramatically improve health care and its significant financial implications. While the future impact of genetics on clinical dentistry was foreseen by a number of scientists and clinicians, fewer foresaw the need for dentists to play a role in genetic counseling aspects of care.

Advances in DNA technology and knowledge of genomic structure and function will help shape future clinical diagnostic and treatment strategies. The successful development and implementation of these innovations will depend upon practitioners’ being educated in scientific and genetic principles as well as their being proficient in assessing and disseminating new forms of genetic information. Available knowledge and technologies are only clinically valuable when they are used by appropriate user groups as recommended. Often there are differences between scientific, public, and professional knowledge about risk factors and clinical incorporation of this knowledge in preventative regimens. Health promotion and education can narrow these gaps.

Education of clinicians will need to incorporate not only genetic concepts, statistics, and epidemiological principles, but also ethical and social aspects that may be unique to genomic medicine. It will be important to target students of dental and affiliated schools (e.g., dental hygiene) as well as their faculties. In addition to care providers and educators, education of advisory boards and policymakers will also be important. While this may appear a daunting challenge, collaborations with health care professionals from other disciplines and organizations may provide valuable insight and expertise (e.g., National Coalition of Health Professional Education in Genetics). In addition to educating professional care providers, communities will also need to be educated and prepared to participate in the transitions that will come if genetic medicine is to effectively integrate into clinical practice.

Clinicians serve at the interface between science and care. While there is a clear need to effectively communicate between these two arenas, care must be taken to appreciate how concepts and information are conveyed. Scientific nomenclatures and terminologies often have attitudinal components. For example, the term “mutation” may technically describe any DNA change, but often the term is used in a deleterious context. While scientists and researchers are trained to approach scientific testing with a rigorous adherence to principles and terminologies, clinicians must often interface between the rigorous scientific world and the clinical environment, translating scientific information to individual care and patient education. It is important to have the sensitivity to avoid insulting or offending individuals when addressing innate characteristics of their biological constitution.

Lack of genetic training is a commonly identified problem for all health professions. Most practitioners have received only a few hours of genetic
training. Health professions schools are attempting to introduce genetic content into existing training curricula, but this is often a slow process because curricula are already overcrowded. In addition to the targeted education of new students, there is a need to increase the genetic content within continuing education programs to reach current care providers and to address genetic issues emerging in current practice.15,16 The ability for care providers and consumers to make informed decisions will increasingly necessitate an understanding of a number of genetic concepts and principles. One of the most important will be an understanding of genetic variance and its role in disease susceptibility.

Genetic Variance and Disease Susceptibility

Increasingly it is apparent that there is a genetic basis for many if not most human diseases. Genetics will become integrated into health care in all medical specialties, including oral medicine and its specialties. At the level of public health, genetic information will become increasingly important in research, policy, and program development.37,68

There are approximately 4,000 genetic diseases, and it is estimated that approximately 30 percent of these affect the head and neck region and are therefore of potential interest to dental clinicians. Understanding the genetic contribution to these diseases should lead to better diagnostic tests as well as etiological-based treatments.

The human genome is characterized by millions of genetic variants, some of which are determinants of disease susceptibility. A major challenge for genomic medicine will be to determine which of these genetic variants have health care applications. Applications of genetic information to health care paradigms will reflect in large part the manner in which genetic variance contributes to health and disease. Clinicians will need to appreciate that the genetic contributions to risk for a given disease can and do vary dramatically. While most people are familiar with the genetic paradigm of mutations causing Mendelian diseases, human genetic variation is also associated with the more prevalent chronic diseases that have major public health impact. Successes in identification of the genetic basis of rare, Mendelian disease genes fueled the drive to identify the genetic basis of more common diseases. The focus of genetic testing is now expanding from detection of relatively simple yet rare Mendelian disorders (diagnostic testing) to risk prediction for more common, genetically complex health problems (susceptibility testing).

To have a realistic understanding of genetic testing, it is important to recognize and understand the differences between Mendelian diseases and the more complex polygene and multifactorial diseases.25,69,70 Although genetic variation at the nucleotide level is an important yet incompletely understood determinant of disease susceptibility, other factors including environmental and sociocultural influences also modify the risk of disease. With increasing knowledge of the human genome, the functional interrelationships of gene products with each other and with the physical and social environment are becoming understood. As the convergence of technology with enhanced understanding of genes and disease continues, dental clinicians will be faced with a complex array of new technologies and types of information.

Genetic Medicine: Clinical Implications and Applications for Dental Practice

As our understanding of disease in general and oral diseases specifically changes, genetic concepts and principles are becoming clinically relevant for oral health care practitioners.53,54,60,61,63-65,71-83 Knowledge of the individual genetic characteristics of patients will likely be important factors in the diagnosis of disease risk and susceptibility as well as in predicting response to treatments. Recent advances in micro-array and parallel technologies allow large-scale analyses of gene expression. This information may be combined with methods that identify genetic variants to characterize oral pathologies.

While gene expression assays are currently mainly research tools, these or newer adaptations will probably see clinical applications for disease conditions in dentistry. It is likely that genetic characterization of oral pathologies such as cysts, tumors, and cancers will find clinical applications. In addition to traditional histological descriptions, genetic sequence and expression information will likely be contained in pathology reports in the future, helping assess le-
sion characteristics such as propensity for aggression, recurrence, and treatment responses. Treatment approaches may encompass targeted pharmacologic manipulation of physiological responses and directed tissue regeneration, replacing traditional dental repair procedures. Because of unique aspects of oral anatomy and physiology, gene therapy may become a tool in the therapeutic protocols for oral medicine. Such technologies may be realized in the clinical practices of today's dental students.

Genetic Testing and Its Considerations: Diagnostic, Susceptibility, and Screening Tests

While genetic principles have long been applied to diagnostics in, for example, the study of syndromes, they have not been broadly applied to most dental practices. Dental care in the future will rely increasingly upon genetic testing to identify genetic variants that affect disease risk and susceptibility as well as response to different treatment regimens. Currently it is possible to identify specific gene mutations that cause a variety of tooth-related genetic diseases including amelogenesis imperfecta, dentinogenesis imperfecta, and hypodontia. Significant dental pathology is, however, associated with several hundred monogenetic diseases. The name “monogenetic” implies that alteration of a single gene can be causal for a condition, and a single gene defect has been identified for many monogenetic conditions, including those shown in Table 1. In general, Mendelian types of diseases tend to be uncommon on a population level, but they are highly prevalent in certain families.

In contrast to the usually uncommon monogenetic conditions described in Table 1, the most prevalent forms of dental disease and developmental pathology are genetically more complex diseases. Increasingly there is a recognized need for genetic studies to help develop diagnostic and treatment strategies for common dental diseases. For example, fol-

Table 1. Monogenetic conditions of dental importance. The corresponding OMIM number is provided for each clinical condition and for the corresponding gene mutated.

<table>
<thead>
<tr>
<th>Condition</th>
<th>OMIM Number</th>
<th>Gene Mutation</th>
<th>OMIM Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amelogenesis imperfecta 1</td>
<td>301200</td>
<td>amelogenin (AMELX)</td>
<td>300391</td>
</tr>
<tr>
<td>Amelogenesis imperfecta 2</td>
<td>104500</td>
<td>enamelin (ENAM)</td>
<td>606585</td>
</tr>
<tr>
<td>Dentinogenesis imperfecta 1</td>
<td>125490</td>
<td>dentin sialophosphoprotein (DSPP)</td>
<td>125485</td>
</tr>
<tr>
<td>Osteogenesis imperfecta IV with DI</td>
<td>166220*</td>
<td>collagen 1A1 (COL1A1)</td>
<td>120150</td>
</tr>
<tr>
<td>Osteogenesis imperfecta IV with DI</td>
<td>166220*</td>
<td>collagen 1A2 (COL1A2)</td>
<td>120160</td>
</tr>
<tr>
<td>tricho-dento-osseous syndrome</td>
<td>190320</td>
<td>distal-less 3 (DLX3)</td>
<td>600525</td>
</tr>
<tr>
<td>hypodontia</td>
<td>106600**</td>
<td>homologue of drosophila muscle segment</td>
<td>142983</td>
</tr>
<tr>
<td>hypodontia</td>
<td>106600**</td>
<td>paired domain gene 9 (PAX-9)</td>
<td>167416</td>
</tr>
<tr>
<td>oligodontia</td>
<td>604625</td>
<td>paired domain gene 9 (PAX-9)</td>
<td>167416</td>
</tr>
<tr>
<td>ectodermal dysplasia; hypohidrotic</td>
<td>300291</td>
<td>inhibitor of kappa light polypeptide gene enhancer in B cells, kinase of, gamma (IKBKG)</td>
<td>300248</td>
</tr>
<tr>
<td>ectodermal dysplasia; anhidrotic</td>
<td>224900</td>
<td>ectodysplasin receptor 1; anhidrotic receptor (EDAR)</td>
<td>604095</td>
</tr>
<tr>
<td>ectodermal dysplasia; Margarita Island Type</td>
<td>225060</td>
<td>Poliovirus receptor related 1 (PVRL1)</td>
<td>60644</td>
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<tr>
<td>ectodermal dysplasia 2; hidrotic</td>
<td>129500</td>
<td>gap junction protein beta (GJB6)</td>
<td>604418</td>
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<tr>
<td>cherubism</td>
<td>118400</td>
<td>SH3 DOMAIN-BINDING PROTEIN 2 (SH3BP2)</td>
<td>602104</td>
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<tr>
<td>celularanofacial dysplasia</td>
<td>119600</td>
<td>RUNT related transcription factor (CBFA1)</td>
<td>600211</td>
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<tr>
<td>Witkop syndrome</td>
<td>189500</td>
<td>MSX-1 transcription factor (MSX1)</td>
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<td>Papillon Lefèvre syndrome</td>
<td>245000</td>
<td>cathepsin C (CTSC)</td>
<td>602365</td>
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<tr>
<td>hereditary gingival fibromatosis</td>
<td>135300</td>
<td>Son of Sevenless-1 (SOS1)</td>
<td>182530</td>
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* ** indicates these clinically similar conditions can be caused by mutation of two different genes. OMIM number indicates catalogue number from Victor A. McKusick’s Mendelian inheritance in man: a catalog of human genes and genetic disorders.
lowing comprehensive reviews of available scientific and clinical literature, a panel of experts recently called for genetic studies to help develop better diagnostic and treatment strategies for dental caries. Emerging disease paradigms also reinforce the concept that the oral cavity must be viewed in the context of the whole body, and common etiologic links are being identified for many complex diseases. Similar genetic underpinnings for diabetes, cardiovascular disease, and periodontitis highlight the need to understand genetic aspects of these links. It is important to appreciate the differences between Mendelian and more complex genetic traits.

When variance in a trait is due to the combined effects of multiple genes, the trait is said to be “polygenic.” When polygenic and environmental factors are both believed to be etiologically important determinants of variance for a trait, it is considered to be “multifactorial.” Our current understanding suggests that common dental pathologies including gingivitis, periodontitis, and caries are multifactorial traits. However, the genetic variants that contribute to overall susceptibility for many common multifactorial diseases are not individually sufficient to cause disease, and it is currently unclear how to integrate information about genetic polymorphisms associated with complex diseases into clinical care scenarios. Many genes that cause Mendelian diseases have been identified, but very few genes underlying genetically complex, multifactorial diseases have been definitively identified.

Genetic tests for simple monogenetic disease causing mutations as well as genetic variants reported to be associated with disease susceptibility in complex traits will be developed and marketed in the coming years. In addition, genetic testing for determining optimal response to pharmacological agents, response to specific treatments, and predictors of prognosis will also become available. The diverse use of genetic testing creates challenges to effectively integrate genetic testing into clinical practice. There is a lack of regulation and expert advisory advice for many genetic testing applications. This will necessitate that clinicians themselves take a more active role in determining the appropriateness of genetic testing.

The Secretary’s Advisory Committee on Genetic Testing (SACGT) stated: “One of the main goals of genetic testing is to improve the health and well-being of individuals and families. The achievement of this goal depends upon the rapid and broad availability of genetic tests as well as their appropriate use. No test should be introduced in the market before it is established that it can be used to diagnose and/or predict a health-related condition in an appropriate way. Thus, the public is best served by ensuring both the adequate oversight of genetic tests and the continued development of genetic tests.”

In evaluating genetic testing, it is important to remember the goal. Genetic tests can be used for diagnostic testing, susceptibility testing, and genetic screening. To be clinically useful, a genetic test must be analytically valid, as well as clinically valid and clinically useful. Many genetic tests determine the presence or absence of a specific nucleotide or nucleotide sequence in the genome of an individual. While the analytical validity of genetic testing should never be taken for granted, with current technologies it is generally possible to reliably characterize genetic variants in individuals. It is therefore generally possible to test individuals for a variety of genetic variants and theoretically to relate these to disease risk and susceptibility. However, the intent of a test should be clear, and it is important to consider how this genetic information will be incorporated into the clinical setting.

In order to evaluate the usefulness of genetic testing, the practitioner must be able to distinguish the differences between 1) genetic testing in a symptomatic individual and 2) genetic testing for an increased susceptibility to a particular disease. The risks and benefits to these populations differ. The technological quality, predictive value, reliability, and validity of each test must be understood. Genetic tests are delivered to the marketplace at a rapid pace, and the value of a test must be considered by both the patient considering testing and the practitioner offering testing.

**Diagnostic Testing**

When a genetic change such as a mutation is directive of a phenotype, the trait is often transmitted as a “simple” monogenetic Mendelian trait. For the conditions listed in Table 1, it is possible to perform a genetic test to definitively determine if an individual has a gene mutation that is responsible for the condition. This information can be used to establish a specific diagnosis and may have treatment implications. For example, cases of amelogenesis imperfecta and dentinogenesis imperfecta may appear to be similar. In addition to genetic forms of these conditions, environmental agents such as tetracycline staining and severe fluorosis may give simi-
lar clinical appearances. However, dental treatments of fluorosis are very different from those for amelogenesis imperfecta. The availability of a reliable genetic test can help diagnose and treat these conditions.

Genetic testing can also provide important information about possible systemic implications of disease. In addition to dental findings, some genetic conditions may have systemic ramifications. Dentinogenesis imperfecta (DI) may arise from mutations in three different genes: dentin sialophosphoprotein (OMIM 125485), collagen 1A1 (OMIM 120150), or collagen 1A2 (OMIM 120160). While the dental presentation of DI may be indistinguishable, associated systemic findings can vary significantly. DI due to mutation of the dentin sialophosphoprotein gene presents without systemic disease (OMIM 125490), while DI due to collagen 1A1 or 1A2 mutations can also present with skeletal deformities and varying degrees of fracture from mild to severe (OMIM 166220). In some cases, associated osseous findings can be highly variable. Identification of the specific gene that is affected can provide important information for management of overall health. In the example of DI, the dental finding can be the most consistent physical finding, and thus may be the initial feature that leads to genetic testing.

In the above examples, the correlation of a gene mutation with a clinical phenotype can be established and genetic tests developed to detect the presence of a gene mutation that is diagnostic for the specific disease trait. The confirmation of a diagnosis can assist with treatment. In such cases, the genetic test is analytically and clinically valid and provides clinical utility. Diagnostic tests for many Mendelian conditions are analytically and clinically valid; however, for many of these conditions, better treatments are not yet available. Unfortunately, genetic testing is not commercially profitable for some rare Mendelian traits, and hence, testing may not be available outside of a research-type laboratory.

Susceptibility Testing

While there have been dramatic successes in identification of genetic mutations responsible for simple Mendelian conditions, most human diseases are genetically more complex. Genetically complex conditions arise from the contribution from multiple individual genes and environmental agents. It is often difficult to quantify the contribution of a single gene allele to disease susceptibility, and therefore a simple cause and effect relationship cannot be established. Genetic variants reported to be associated with disease states are often common genetic variants in the population, occurring in both affected and unaffected individuals. While it is possible to demonstrate that a specific genetic allele is statistically associated with a disease state more frequently than expected by chance, for many complex genetic diseases, it is not currently clear how genetic information obtained in research studies can be used to improve clinical care. Nonetheless, certain genetic susceptibility tests are being offered for common complex diseases.

Dental caries and chronic periodontitis appear to have significant genetic components; however, to date, clinically validated genetic variants that have demonstrated clinical utility have not been identified. Dental care providers should be aware that there is some controversy about whether and how genetic polymorphisms identified in research studies can and should be used for clinical care. Several expert panels have reinforced the important principles that genetic variants should demonstrate clinical validity and clinical utility before they are introduced to clinical practice. Clinicians should be aware that although criteria for establishing these benchmarks are now being discussed, formal regulation of genetic testing and its application to clinical care are not stringently regulated in most cases. Two organizations do regulate certain aspects of genetic testing: the FDA and CLIA (Clinical Laboratory Improvement Amendments). Most current CLIA and FDA guidelines address analytic validity for genetic testing—that is, that a laboratory assay identifies a specific genetic variant accurately and reproducibly. With current technologies, analytical validity of genetic tests is becoming standard; however, the clinical validity and clinical utility of genetic variants associated with complex diseases are often difficult to demonstrate.

Many chromosomal and Mendelian genetic conditions have been greatly served by clinically valid and clinically useful genetic testing. However, interpretation of genetic test results, particularly for complex genetic diseases, can be problematic. In a recent review of genetic variants reported to be significantly associated with complex disease phenotypes, the vast majority were not reproducible. The point here is that clinicians and patients must keep realistic expectations of genetic testing. It is critical to recognize the difference between diagnostic and susceptibility testing. Unfortunately, our current ability to identify the presence/absence of genetic vari-
nants in individuals far exceeds our ability to provide a meaningfully clinical interpretation and clinical utilization of this information for genetically complex traits.

Currently, the genetic basis of multifactorial diseases is poorly understood and has not dramatically impacted health care. However, greater understanding may permit presymptomatic assessments of risk in the future. In such a scenario, genetic susceptibility no longer indicates a deterministic event, a predestined outcome, but rather a situation of increased risk that, if identified, may be modified, provided an intervention to reduce the chance of disease is available. Susceptibility testing could provide a means of targeted disease prevention.

In addition to disease susceptibility, understanding gene-environment interactions in health and disease carries broad health care implications. Individual differences in drug metabolism and healing responses are influenced by genetic factors. It is likely that in the future it will be possible to genetically characterize individuals to optimize drug regimens, and this is likely to become an important part of optimizing treatment to an individual’s biologic makeup. As such testing becomes available, access to care and treatment will be an increasingly important social issue.

However, other social issues can arise as determinants of genetic susceptibility are identified. If employers are responsible for providing health care, what are the responsibilities of their employees? If certain individuals are found to have genetically determined or genetic behavioral predisposition to environmental agents that increase disease risk, where are the boundaries for what a care provider can expect or demand from a potential patient? What are the bounds of individual responsibility? If an individual is found to have a genetic makeup that places him or her at significantly greater risk for chronic periodontitis or oral cancer, can an employer or society demand certain behavioral modifications (such as cessation of cigarette smoking) or be permitted to deny medical coverage? These are complex and difficult social and ethical questions that may ultimately need to be addressed.

**Genetic Screening vs. Genetic Testing**

Genetic screening differs from genetic testing in that it targets populations rather than at-risk individuals. Genetic screening generally is performed to detect future disease risks in individuals or their progeny for which established preventive interventions exist. Examples of genetic screening include newborn screening for phenylketonuria, carrier screening for sickle cell disease, and prenatal screening of fetal cells to detect chromosomal or other congenital abnormalities. Genetic information will increasingly be used in population screening to determine individual susceptibility to common disorders such as heart disease, diabetes, and some cancers. Such screening will identify groups at risk so that primary-prevention efforts (e.g., diet and exercise) or secondary-prevention efforts (early detection or pharmacologic intervention) can be initiated. Such information could lead to the modification of screening recommendations, which are currently based on population averages (e.g., screening of people over fifty years of age for the early detection of colorectal cancer).

There are concerns that if screening tests become routine practice, individuals may be pressured to undergo testing that they would not choose to undergo in a different context. It is possible that discrimination and/or stigmatization against individuals and groups who are the subjects of genetic screening because of their racial, ethnic, or geographic origin could occur. A number of factors must be evaluated in determining whether a particular screening test should be implemented, including the purpose of the screening test, the test’s analytical validity, clinical validity, and clinical utility, the social implications of the test, and the economic cost of the screening test.99

**Surveillance**

Nearly every human disease has a genetic component that will eventually be relevant to disease prevention. Surveillance will be important to gathering the information needed to study the public impact of genes on the population; to determine the prevalence, distribution, and frequency of disposing genetic variation; to track morbidity and mortality associated with genetically linked diseases; to identify modifiable risk factors for disease; and to track efficacy of intervention strategies. It will be important to understand how different genetic disease models affect susceptibility. The relative contributions of genes and environmental factors will vary significantly for different diseases, as will needs and methods for surveillance in different populations. From a public health perspective, diseases and conditions of greatest concern will be those that result from a more complex interaction between single or multiple ge-
Genetic variants and factors in the social and physical environment. To attain the necessary power to detect and substantiate the role of genetic variants in disease risk, susceptibility, and intervention strategies, it will be necessary to have broad community support and acceptance.

While important for public health care, and ultimately for optimization of individual health care, surveillance carries social risks. Social risk in health behavior is the danger that individuals will be socially or economically penalized should they become identified with an expensive, disfavored, or feared medical condition. Social risk has two distinct components: the threat and the perception of risk. Social risk will influence acceptance of surveillance whenever the social construction or economic cost of a disease creates at least the perception of risk, which alone or in combination with other factors outweighs the benefits of obtaining a diagnosis or therapeutic care. In creating the Public Health Service at the turn of the twentieth century, the congressional mandate said almost nothing specifically about genetics. At present no systematic national system of surveillance for genetic diseases exists in the United States.

### Regulation

The pace and generality of the discovery and dissemination of genetic information have outpaced regulatory bodies that may have been traditionally relied upon to protect the public interest in clinical and in medico-legal scenarios. While issues related to access to care and privacy are generally appreciated, issues related to standards of care are not.

Determination of clinical validity and clinical utility of genetic tests is complex and often difficult. It will be important for clinicians and the lay public to participate in the development of appropriate guidelines for the safe and efficacious integration of genetic medicine into clinical practice. However, few individuals have received the formal genetics training that provides the requisite knowledge to do so. Public health policymakers are beginning to discuss the appropriate role of genetic testing for identification of personal risk in the adult population. Guidelines that have been developed for the use of testing in some cases (e.g., BRCA mutations for breast cancer and genes for some forms of colon cancer) are coming almost exclusively from professional societies and groups of investigators. No professional dental society has offered recommendations or guidelines for genetic testing.

### Summary

Genomic medicine is transforming health care from a reactive clinical approach to a proactive paradigm that may permit individualization of care to optimize health and well-being. In addition to the broad health implications of genomic medicine, there are also significant economic ramifications. Those societies that are able to effectively integrate genetic medicine into health care systems to the point where the work force is healthier will have an economic advantage over competing societies. Genetic medicine thus carries real economic and political implications. While some may feel that these developments will not impact clinical dentistry, this may be a shortsighted view.

As we understand more about the genetic basis of growth and development, as well as genetic susceptibility to disease, it is apparent that the health of the oral cavity is developed and maintained in association with a systemic physiology. As links between periodontitis and systemic conditions such as cardiovascular disease, diabetes, and weight loss emerge and are understood, maintaining oral health may be increasingly viewed in a systemic context. Consequently, genetic factors will become increasingly more relevant. Even in cases where genetic testing may not directly impact dental structures, patients can be expected to have genetic testing performed for a variety of diagnostic, susceptibility, and treatment intervention strategies. To contribute to the health and well-being of their patients, dental clinicians will need to understand and appreciate the appropriate role of genetics in health care.

In this post-genomics age, we will find ourselves barraged by information with little guidance about how to select genetic tests, interpret the results, and consult with families to make a shared decision about genetic testing. Genetic testing is complicated and can be intimidating for patients as well as clinicians who are expected to be well informed. Information about one family member may directly impact other family members; standards for privacy and assurance of confidentiality for protection of genetic information are fragile; and basic and postgraduate training in genetics is scarce. There are significant pressures to integrate genetic information into clinical care, yet there is often little precedent. Indiscriminate genetic testing may result in a backlash against testing that may otherwise significantly improve health care. Advances in genomic
information and new technologies often outpace regulatory guidance for appropriate integration into existing health care paradigms. With genomic medicine come the realistic expectations to personalize health care, yet this divergence from one-size-fits-all medicine comes at a price. Especially when considering the genetic basis of complex traits, it is difficult to quantify the risk associated with disease-associated polymorphisms. Consequently, it is difficult to assess the clinical validity and clinical utility of tests on an individual basis. To ensure appropriate use and informed consent for genetic testing, both clinicians and consumers will need to understand these issues. A basic understanding of genetics will be essential. As these challenges are addressed, it will be important to extend the services of genomic health care to all members of society.

Clearly, dental clinicians will need to participate in this process both as health care providers and as recipients of services themselves. To fulfill these roles, dental practitioners will need to become familiar and comfortable with the technological and informational advances yielded from the human genome project, as well as the psychosocial issues involved in decision making regarding genetic testing for individuals and families.

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