Transfer of Advances in Sciences into Dental Education

Genetic Testing Considerations for Oral Medicine

Thomas C. Hart, D.D.S., Ph.D.; Robert E. Ferrell, Ph.D.

Abstract: The availability and integration of genetic information into our understanding of normal and abnormal growth and development are driving important changes in health care. These changes have fostered the hope that the availability of genetic information will promote a better understanding of disease etiology and permit early, even pre-symptomatic diagnosis and preventative intervention to avoid disease onset. Expectations for this proactive health care approach are fueled by the technological and scientific advances that have fundamentally changed how we perceive human diseases. Among the clinical applications of this information, genetic testing applications are likely to expand significantly and may broadly impact the clinical practice of dentistry. In this changing environment, it is vital that dental care providers, policymakers, and consumers become aware of important issues related to genetic testing and the incorporation of genetic information into the diagnosis and treatment of common diseases that involve the oral cavity. We must also guard against unrealistic expectations and calls for genetic tests that are not valid. To realize the promise of this new molecular genetics, we must understand the possibilities and responsibly incorporate newly emergent technologies into the evolving discipline of dentistry. This paper overviews many of the important issues that need to be considered in the application of genetic testing to oral medicine.

Dr. Hart is Associate Professor, Department of Oral Biology and Medicine, School of Dental Medicine, and Dr. Ferrell is Professor, Department of Human Genetics, Graduate School of Public Health, both at the University of Pittsburgh. Direct correspondence and requests for reprints to Dr. Thomas Hart, University of Pittsburgh, School of Dental Medicine, 614 Salk Hall, 3501 Terrace Street, Pittsburgh, PA 15090; 412-383-7695 phone; 412-624-3080 fax; hart@sdmgenetics.pitt.edu.

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Although medical genetics has been an important part of health care for many years, it has not been a common component of dental practice in most dental offices. Dentists usually receive little formal genetics training. Consequently, many dentists may not be familiar with medical genetics outside the context of the team approach to the treatment of orofacial clefting. The association of syndromology and genetic counseling with clinical dentistry has primarily occurred in the restricted setting of medical centers and not as part of the traditional dental office. While dentists are generally familiar with a few, rare genetic conditions that affect the teeth, such as amelogenesis imperfecta and dentinogenesis imperfecta, genetic testing has not been a significant part of the clinical care offered by most dentists. In part due to lack of training and the lack of perceived need and available applications, most dentists have little contact with medical genetics. As a result, many dentists are not appraised of the significant changes occurring in clinical and molecular genetics that are likely to have broad implications and applications for clinical dentistry.

Dental clinicians have historically made significant contributions to characterizing dental and craniofacial findings in many genetic conditions. In fact, Dr. Robert Gorlin, an oral pathologist, made significant contributions to the emerging field of clinical dysmorphology and syndromology by his cataloguing of disorders. Dr. Gorlin’s text Syndromes of the Head and Neck remains an important resource for medical genetics. Although not generally appreciated, the dental field has experienced periodic calls to integrate medical genetics into dental training. While certain members of the dental profession have been proponents of integrating genetics into the training and practice of dentistry, such recommendations have gone largely unheeded—in large part due to the general perception that medical genetics was of limited utility to the clinical practice of most dentists. Such knowledge was not regarded as essential to the day-to-day practice of dentistry. Realization of the important role of genes in disease etiology now challenges this traditional perspective. The sequencing and annotation of the human genome carry broad practical implications for the application
of genetic testing to the mainstream practice of dentistry. These developments are occurring at a time when many in the dental profession are calling for oral health to be viewed as an integral part of a continuum of overall systemic health.6,7

As a result of the significant changes occurring in medical genetics and related fields of research, the scope of genetic testing is rapidly expanding. Traditionally genetic testing has been utilized for diagnostic purposes: to detect chromosomal alterations (cytogenetics) and gene mutations for simple Mendelian conditions. The past decade has witnessed the identification of hundreds of rare genetic conditions, including many with dental importance, such as amelogenesis imperfecta, dentinogenesis imperfecta, Papillon Lefevre syndrome, and hypodontia/anodontia. The great change occurring in medical genetics is that genetic testing may soon be used to test for disease risk/susceptibility to such common diseases as cardiovascular disease, diabetes, and chronic periodontitis. It may also be practical to determine individual risk for orofacial developmental anomalies such as clefting, as well as for some forms of cancer such as oral squamous cell carcinoma. In addition to diagnostic and susceptibility testing, genetic testing may be used to gauge patients’ prognosis and predict their response to specific medications. As our understanding of molecular determinants of growth and development increases, it may become feasible to predict patterns of craniofacial growth and development, with implications for the diagnosis and treatment of anomalies of craniofacial development such as some forms of temporomandibular joint disorder and malocclusion. Clearly, the expansion of genetic testing to the arena of predictive testing of disease risk, prognosis, and response to therapy will be an important component of health care in the future. When this broader umbrella of genetic testing is considered, it is reasonable to envision its playing a significant role in the mainstream of routine dental care.

Fundamental Changes in Medical Genetics

As a result of our increasing understanding of the human genome and the functional interrelationships of gene products with each other and with the environment, it is increasingly evident that most human diseases are influenced by heritable variations in the structure and/or function of genes.8 These developments have led to expectations that it will be possible to quantitate genetic components of disease

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**Glossary of Genetic Terms**

- **Allele**: conventional abbreviation for “allelomorph.” Refers to the different forms or DNA sequences that a gene may have in a population. One of a group of different forms of a gene that occur alternatively at a given locus.

- **Genetic Test**: the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers, and establishing prenatal and clinical diagnosis or prognosis. Prenatal, newborn, and carrier screening, as well as testing in high-risk families, is included. Tests for metabolites are covered only when they are undertaken with high probability that an excess or deficiency of the metabolite indicates the presence of heritable mutations in single genes. Tests conducted purely for research are excluded from the definition, as are tests for somatic (as opposed to heritable) mutations and testing for forensic purposes.19

- **Locus**: the position in a chromosome of a particular gene or allele.

- **Mutation**: a relatively permanent change in hereditary material involving either a physical change in chromosome relations or a molecular change in the nucleotide composition of a sequence that makes up a gene.

- **Polymorphism**: a locus in which two or more alleles have gene frequencies greater than 0.01 in a population. When this criterion is not fulfilled, the locus is considered monomorphic.

- **STRP (short tandem repeat polymorphism)**: a type of genetic variation (polymorphism) in populations that consist of small repeat units (usually two, three, four, or five nucleotide base pairs) that occur in tandem. Also called a microsatellite repeat polymorphism.

- **SNP (single nucleotide polymorphism)**: polymorphisms that result from variation at a single nucleotide.

- **Variable clinical expression**: a trait in which the same genotype may produce phenotypes of varying severity or expression.

- **Allelic heterogeneity**: condition in which different alleles at a locus can produce variable expression of a disease.

- **Locus heterogeneity**: refers to conditions in which mutations in different genes (loci) can produce the same disease phenotypes.
risk prior to the onset of a variety of clinical diseases. It is anticipated that the presymptomatic identification of at-risk individuals will permit the implementation of preventative intervention strategies, potentially enabling avoidance of disease entirely.9-11 These hopes and expectations have been encouraged by media reports that sometimes oversimplify the issues and lead to false expectations among the public. Although it has long been recognized that DNA encodes the genetic blueprint that guides growth and development, sequencing of the human genome has been heralded as the critical step that will permit us to understand how genes act. While this is a simplistic conceptualization of a complex and multifaceted issue, it is not without scientific merit.

As annotation of the human genome progresses, it is evident that there is considerable inter-individual variability in the primary sequence of the human genome. It is likely that this variation is an important determinant for the differential susceptibility to disease as well as differences in disease outcomes observed between individuals. The mapping and sequencing of the human genome have facilitated the identification of numerous specific genetic changes (mutations) primarily responsible for a variety of rare, “simple” Mendelian genetic conditions. These are catalogued in a World Wide Web database: Online Mendelian Inheritance in Man (OMIM).12 This database, which grew out of Dr. Victor A. McKusick’s catalog of inherited human phenotypes and adapted for the web by the National Center for Biotechnology Information (NCBI), contains textual information and references for thousands of genetic conditions and associated gene mutations. It also contains copious links to MEDLINE and a variety of other Internet-based genetic resources. Success in identifying the genetic basis for simple genetic conditions is dramatically illustrated by the almost exponential increase in the number of additions to the OMIM database over the past twenty years.

In contrast to the relatively rare simple Mendelian disorders, the majority of the human disease burden is attributable to more complex diseases such as diabetes and cardiovascular disease (CVD).13 Many of these conditions are chronic, progressive in nature, and have a later age at disease onset. While epidemiological studies have long suggested that environmental and behavioral factors are etiologically important in these conditions, the past two decades have witnessed a continued emergence of support for a significant role for genetic susceptibility in many complex diseases. While these more common diseases have a significant genetic component, the mechanisms by which genes contribute to these conditions are more complex than for simple Mendelian disorders. As a result of the confluence of factors including gene identification and characterization, integrated genetic and proteomic studies, and the development of molecular epidemiology, there is now a focused effort to identify the genetic basis of disease susceptibility for many common, complex diseases.14 Although success in genetic studies of these complex conditions has not yet equaled the success in studies of simple genetic conditions, significant resources are now being allocated to the identification of genetic susceptibility to many common, complex diseases.

In addition to providing the requisite information to characterize individuals with respect to disease susceptibility, the continued characterization of the human genome should provide information to understand biological responses to a range of environmental agents (including diet, physical activity, infectious agents, and specific medications). Consequently, the ability to identify specific genetic variants on an individual level will have broad implications and applications for health care. As these genetic variants may be directly assayed from an individual’s DNA, their characterization falls under the general purview of genetic testing. A significant change now occurring in medical genetics is that the focus of DNA testing has expanded from the realm of simple genetic conditions such as syndromes to the much more prevalent complex genetic conditions such as CVD, diabetes, and in the dental field, periodontitis, oral clefting, squamous cell carcinoma.

While specific applications of genetic testing to dentistry may be debated, it is reasonable to predict that genetic testing will become a routine part of dental practice, and thus, dental care providers must become familiar with the principles and concepts of genetic testing. Although exciting, the application of genetic medicine to clinical dentistry must be tempered by the real challenges that face the responsible and efficacious integration of genetic testing, particularly for disease susceptibility, into dental practice. While the genetic basis of human disease is becoming evident, the application of this knowledge to the diagnosis and treatment of these diseases remains years away in most cases. Because the field of medical and molecular genetics has evolved so rapidly, few consumers or health care pro-
providers are adequately versed in genetic issues to effec-
tively integrate genetics into emerging health care paradigms.\textsuperscript{15,16} This paper discusses a number of genetic concepts and principles that the dental community will need to discuss to appreciate the importance of genetic testing for oral diseases as well as its limitations.

**Gene Identification**

As sequencing and annotation of the human genome are completed, the full complement of human genes will be identified.\textsuperscript{17} A striking characteristic of the genome is the degree of variability in the DNA sequences between individuals. This genetic variation is believed to be a primary determinant of the physiological and phenotypic differences between people. The availability of genetic information should facilitate understanding of the gene-protein, protein-protein, and protein-environment interactions that underlie normal and abnormal (including disease) physiology, growth, and development. This knowledge should provide the framework for the development of pre-symptomatic testing and intervention strategies that ameliorate undesirable outcomes. This genetic medicine paradigm is summarized in Figure 1. In the case of simple genetic conditions, when disease-causing mutations are identified, genetic information does often permit diagnostic testing and family counseling (Figure 2). Genetic testing can confirm clinical diagnoses, provide information to predict prognosis, and in some cases help clinicians select the most appropriate treatment.\textsuperscript{18}

Although genetic medicine is ultimately expected to provide genetic information to more effectively treat or prevent disease, this is not currently practical for most genetic diseases. A major reason treatment intervention lags behind diagnostics in medical genetics is because we do not have a sufficient understanding of the molecular determinants of normal and abnormal pathobiology to enable development of enhanced intervention strategies. This is likely to change in the future. However, gene identification is only the first step towards understanding human disease at the most fundamental level. In general, understanding how the products of genes act to cause disease provides a major challenge that must be met before development of more effective treatments can occur. Genetic testing itself can be clinically useful even before a comprehensive understanding of disease is available.

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**Figure 1. General paradigm for genetic medicine**

*Note:* Gene isolation provides the first step towards understanding human disease at the most fundamental level. After genetic variants are characterized, diagnostic tests can be developed to identify presence of specific forms of the target gene. In addition, understanding of the basic biologic defect will emerge with knowledge of how individual gene products function alone and in tandem with other genes and with environmental factors to cause normal and abnormal growth and development. Ultimately, this genetic information should provide the cornerstones for preventative medicine predicated on early diagnosis and clinically efficacious intervention strategies.
Genetic testing for complex diseases is more problematic at this time. With current technologies it is possible to identify genetic variation (polymorphisms) at targeted genomic sites in specific individuals. While this may be considered “genetic testing,” the clinical validity and utility such a test provides, particularly for the clinical care of an individual, must be demonstrated. The utility of genetic information to predict disease risk is predicated on the identification of genetic polymorphisms that are, in fact, associated with disease risk in a meaningful way. In contrast to the direct relationship between genetic mutations and the occurrence of symptoms in simple genetic diseases, the relationship between genetic polymorphisms and the occurrence of symptoms in complex diseases is much more difficult to validate. However, as emerging disease paradigms place increased emphasis on identification of genetic components of disease susceptibility for complex diseases, this type of genetic information is likely to play an important role in disease management. Consequently, it is likely that an increasingly complex array of genetic testing applications will emerge, and some will have applications for dental practice. As the general public becomes increasingly aware of genetics from a variety of sources, it is important that health care providers are knowledgeable and have critically evaluated appropriate information.

**Figure 2. Genetic testing paradigm for simple vs. complex diseases**

Genetic Information and Personalized Medicine

For many, genetic testing conjures up the image of a diagnostic test that efficiently determines the presence or absence of a specific disease-causing mutation, thus permitting definitive determination of the presence or risk of a genetic disease. While genetic testing is diagnostic for many clearly inherited diseases (Table 1), these are generally rare conditions, and in many cases, identification of the underlying gene mutation does not yet influence treatment decisions. Genetic tests will continue to be used for the diagnosis of single gene diseases, but will also likely be used to begin to quantitate an individual’s risk for more complex genetic diseases. Identification of human genes and characterization of the genetic variation associated with each should allow investigators to identify genes that are etiologically important determinants of risk for complex human diseases. This information will permit sub-classification of diseases, based on etiology. Improved nosology should help researchers identify and evaluate more appropriate treatments and ultimately develop personalized therapies based on the genetic characteristics of an individual.
Table 1. Examples of clinical disease states due to simple genetic etiology

<table>
<thead>
<tr>
<th>Disease</th>
<th>Genetic Basis</th>
<th>Clinical Trait</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypodontia</td>
<td>Mutation of MSX1 (chromosome 4)</td>
<td>Varying degree of hypodontia</td>
<td>Hypodontia present as an isolated clinical finding, but is also associated with a number of genetic syndromes.</td>
<td>61, 62</td>
</tr>
<tr>
<td></td>
<td>Mutation of PAX9 (chromosome 14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amelogenesis Imperfecta</td>
<td>Mutation of amelogenin gene chromosome X, mutation of enamelin gene chromosome 4</td>
<td>Defective enamel</td>
<td>Emerging genotype-phenotype associations. Other autosomal forms exist, genes not yet identified.</td>
<td>63, 64</td>
</tr>
<tr>
<td>Dentinogenesis Imperfects</td>
<td>Mutation of any of 3 genes: collagen 1A1 (chromosome 17), collagen 1A2 (chromosome 7), or dentininsalophosphoprotein (chromosome 4)</td>
<td>Defective dentin</td>
<td>Dentin defect may occur as isolated finding or associated with defects of other tissues, including bone fragility, blue sclera, and joint hyperextensibility.</td>
<td>14, 15, 16</td>
</tr>
<tr>
<td>Papillon-Lefevre syndrome</td>
<td>Mutation of cathepsin C gene chromosome 11</td>
<td>Palmoplantar hyperkeratosis</td>
<td>~50 different cathepsin C mutations identified</td>
<td>65</td>
</tr>
<tr>
<td>Tricho-dento-osseous syndrome</td>
<td>Mutation of distal-less 3 gene chromosome 17</td>
<td>Enamel hypoplasia, taurodontism, kinky/curly hair phenotype, increased thickness and density of bone</td>
<td>Variable clinical expression of hair, teeth, and bone</td>
<td>66</td>
</tr>
</tbody>
</table>

Note: For each disease, “Genetic Basis” indicates specific gene(s) identified to be mutated with each clinical condition. “Clinical Trait” lists the cardinal clinical features of each condition.

Table 2. Examples of complex genetic diseases in dentistry

<table>
<thead>
<tr>
<th>Disease</th>
<th>Evidence of Genetic Basis</th>
<th>Clinical Trait</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic periodontitis</td>
<td>Twin studies</td>
<td>Destruction of periodontium</td>
<td>Genetic and environmental factors. Inflammatory response polymorphism may affect susceptibility; environmental agents include gram negative microbes, tobacco smoking, possibly high lipid diet. Specific genetic polymorphisms proposed for many genes including TNFα, IL-1α, IL-1β, VDR and Fc-gammaRIIIb.</td>
<td>52</td>
</tr>
<tr>
<td>Dental caries, childhood</td>
<td>Twin studies</td>
<td>Enamel demineralization, dentin demineralization, and cavitation</td>
<td>Mutans streptococcus, dietary sugar, and other carbohydrates. Behavioral components, oral hygiene. Genetic factors not unequivocally identified.</td>
<td>55</td>
</tr>
<tr>
<td>Cleft lip/ palate</td>
<td>Twin studies, Family studies</td>
<td>Orofacial clefting</td>
<td>Genetic and environmental factors implicated in etiology. More than 250 forms of orofacial clefting identified. Genetic polymorphisms in TGFB, other. In addition to functional polymorphisms, gene mutations, e.g., Msx1, may also be etiologic in some forms.</td>
<td>56, 57, 67</td>
</tr>
<tr>
<td>Oral squamous cell carcinoma</td>
<td>Molecular progression model of cancer</td>
<td>Continuum from dysplasia to invasive &amp; metastatic squamous cell carcinoma</td>
<td>Genetic basis complex, including polymorphisms of xenobiotic metabolizing enzymes. Environmental factors include cigarette smoking, other forms of tobacco, betel nut, alcohol, and human papilloma viruses. In addition to functional polymorphisms, somatic mutations, e.g., p53, may be etiologic as genetic damage occurs as part of molecular progression model.</td>
<td>58, 59, 60</td>
</tr>
</tbody>
</table>

Note: For “Complex” genetic conditions, environmental agents are those demonstrated to be etiologically associated with the condition. “Genetic Basis” lists genetic polymorphisms reported to be associated with increased risk with disease state in case-control studies. The level of support for a causal role with disease is not demonstrated with the same scientific and clinical rigor as are gene mutations reported for the “Simple” genetic traits. The examples of mutations (e.g., in PLS) and functional polymorphisms (e.g., for chronic periodontitis) illustrate two extremes of a continuum. The genetic basis of some disease states may lie within the extremes of this continuum, such as genetic variants important in some forms of orofacial clefting and oral squamous cell carcinoma, in which genetic mutations, functional polymorphisms, and environmental agents are etiologically important.
Although genetic testing is diagnostic for many simple genetic diseases, the presence of a gene variant reported to be associated with a complex disease is usually not diagnostic, and the clinical utility of such information is difficult to quantitate on an individual level (Table 2). Unfortunately, many expectations of genetic testing are inaccurate, particularly with respect to the types of genetic tests that are emerging and the types of genetic information that will be used to test for genetic susceptibility to complex diseases. It is important that the value and limitations of genetic testing be fully understood. In contrast to the simple Mendelian forms of disease, genetic testing for susceptibility alleles has been less fruitful for more common diseases (prevalence > 1/1,000), and our ability to test for genetic variants far exceeds our ability to apply genetic information in a clinically useful manner.

How to use genetic knowledge to promote health and prevent disease is now being explored. Genetic knowledge could benefit public health on an unprecedented scale, yet initial excitement and optimism must be tempered with the realistic understanding of what is economically and technologically feasible, as well as clinically useful. Genetic testing is different from most other forms of medical testing in that the identification of a particular genetic variant in an individual indirectly provides information about that individual’s close relatives. This leads to legal, social, and ethical issues that are, to varying degrees, unique to medical genetics. Implementation of genetic testing strategies thus has significant social, economic, and political implications. To benefit all members of society, it is essential to develop a framework for the integration of human genetics into the public health practice of dentistry. A key to responsible integration of genetic testing into clinical care is the education of health care providers, patients, and policymakers regarding pertinent genetic principles and concepts.

**Genetic Basis for Disease**

To understand genetic testing, it is necessary to appreciate how genes can cause disease. The human genome consists of three billion base pairs, approximately 3 to 5 percent of which encode genes. Although gene-coding regions are highly conserved, the human genome is characterized by variability in the primary DNA sequence. Many different types of DNA sequence variability have been identified. Approximately 25 percent of the genome occurs as repeated segments of DNA. When the tandemly repeated DNA segment is relatively large (thousands-millions of nucleotides), it is referred to as “satellite” DNA. Tandem repeats of DNA, where the repeated nucleotide unit is several hundred nucleotides, are referred to as “minisatellite” polymorphisms. Smaller tandem repeats of DNA, where the repeated nucleotide unit is two to five nucleotides, are variously referred to as microsatellite polymorphisms and short tandem repeat polymorphisms (STRPs). These STRP types of DNA sequence polymorphisms have been particularly important in gene-mapping studies. These DNA variants generally occur outside of the coding regions of genes and most have no detectable function, so they are sometimes referred to as “anonymous” DNA polymorphisms.

In contrast to STRPs that usually do not occur in the coding region of genes and do not alter gene function, a variety of single nucleotide changes can occur, including substitution of one of the four nucleotides by another, deletion of a nucleotide, or insertion of an extra nucleotide. This common form of genetic variant, called a single nucleotide polymorphism (SNP, pronounced “snip”), can occur in coding regions of genes. When a SNP occurs in the coding portions of genes, it can alter the function of a gene or its product. SNPs are the most common source of variation in the genome and are thought to be responsible for most of the observable biological differences between individuals, including individual differences in disease susceptibility. SNPs are likely to be important in many genetic tests. For an explanation of SNPs, see Box 1.22

Identification of SNPs that influence risk for complex diseases are the driving forces behind intense efforts to establish the technology for large-scale analysis of them. Understanding the relationship between genetic variation and biologic function on a genomic scale is expected to provide fundamental new insights into the biology and pathophysiology of humans, providing the basis for genetic screening, diagnostic testing, and clinical intervention. However, to understand the biological underpinnings for most genotype-disease correlations, it will be necessary to understand how gene products function. The genome sequencing effort has helped spawn the field of proteomics. The sum total of all the proteins expressed in a cell is known as the proteome, and its expression corresponds to the field of proteomics. The
number of different proteins in an organism is much larger than the number of genes. Alternative splicing gives rise to multiple messenger RNAs, leading to the synthesis of multiple proteins from a single gene, and extensive post-translational modification of proteins is common. In biology, functional explanations are the basis for understanding molecular pathogenesis. Consequently, proteins are replacing genes as the entities that need to be catalogued and analyzed in order to understand biological complexity, but the task will not be a simple one.24

Genetic variation impacts all human disease; however, the magnitude of the genetic contribution to susceptibility for specific diseases varies enormously. The role of genetic factors in human disease can be viewed as a continuum: on one extreme, an uncommon DNA variant (mutation) can result in a severe disease phenotype; at the other extreme, a common DNA variant (polymorphism) can result in a very small but measurable change in the function of a gene product, which under certain conditions like environmental exposure or imprudent lifestyle alters the cellular physiology to increase or decrease disease susceptibility. In the case of single-gene disorders, the DNA change is sufficient to “cause” disease, while in the case of more common, genetically complex diseases, the DNA change is not causal, but may in combination with additional genetic and/or environmental factors increase disease susceptibility.

Geneticists have historically distinguished between single-gene disorders, in which a single gene alteration can cause disease, and genetically more complex disease states, in which multiple different genes increase an individual’s disease susceptibility. In the latter case, no one gene contributes enough to cause disease, and the individual contribution of different genes to the disease state is difficult to quantify. The distinction between genetic variants that cause disease and functional polymorphisms that influence disease susceptibility is not merely academic; it has significant implications for genetic testing and for treatment or preventive intervention strategies.

Genotype-Phenotype Correlations

Hundreds of simple Mendelian genetic conditions have been described. Most of these conditions have a clear pattern of inheritance, and the genes responsible for many of these conditions have been identified.12 In these Mendelian diseases, a change in observable features (phenotype) arises as a consequence of mutations in one (dominant) or both (recessive) copies of a gene. While robust correlations between genotype and phenotype are apparent for many simple as well as a few more complex genetic diseases,25,26 a simple one-gene to one-phenotype correlation is not always apparent. Significant variation in clinical phenotype can occur even in Mendelian diseases. As we understand more about the mo-

Box 1. Single nucleotide polymorphisms (SNPs)

SNPs (pronounced “snips”) are the most frequent form of human genetic variation. They occur approximately every 1,000 nucleotides in the human genome. Because only about 3 to 5 percent of a person’s DNA sequence codes for the production of proteins, most SNPs are found outside of “coding sequences” and are thought not to have a functional effect on a person’s health. SNPs found within a coding sequence are of particular interest to researchers as they are more likely to alter the biological function of a protein. Although most SNPs do not produce physical changes in people, scientists believe that some SNPs that occur in certain genes may predispose a person to disease by altering the function of the gene product. SNPs can also influence how a person responds to a particular drug regimen. SNP variation provides the highest-resolution genomic fingerprint for tracking disease genes. Due to recent advances in technology, coupled with the unique ability of these genetic variations to facilitate gene identification, there has been a recent flurry of SNP discovery and detection.

In the example below, the bolded triplets represent a triplet coding region of a gene. An example of a SNP is the alteration of the DNA segment AAAGTTATT to AAGGTTATT, where the third “A” in the first snippet is replaced with a “G.” Since both AAA and AAG code for the amino acid Lysine, this is referred to as a “synonymous” SNP. In contrast, the second case illustrates a “non-synonymous” SNP. Here the second “G” in the first snippet is replaced by an “A,” and the amino acid changes from a glycine to a glutamine.

<table>
<thead>
<tr>
<th>Synonymous SNP</th>
<th>Nonsynonymous SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAAGTTATT to AAGGTTATT</td>
<td>GGA GTTAC to GAA GTTAC</td>
</tr>
<tr>
<td>AAG and AAA both code for Lysine</td>
<td>GGA codes for Glycine, GAA codes for Glutamine</td>
</tr>
</tbody>
</table>
lecular basis of disease, it is apparent that even “simple” genetic conditions are actually complex, and the final phenotype may be significantly influenced by several genetic and/or environmental factors acting on the mutated “gene of major effect.”27,28 Additionally, mutations of the same gene can result in surprisingly different phenotypes. The dramatic clinical variability associated with some forms of craniosynostosis is attributed to the significant effect of modifying genes and the effect of non-genetic factors (environment).29 Clearly, important interactions between genes (gene-protein and protein-protein interactions) and between genes and the environment are poorly understood (see Figure 3).30

These observations reinforce that while it is possible to develop genetic tests for many Mendelian conditions, interpreting these tests can be complicated by variable penetrance, variable clinical expression, and genetic heterogeneity. Mutations in different genes can cause a similar disease phenotype. For example, dentinogenesis imperfecta may result from mutations of the collagen 1A1 gene on chromosome 17,31 the collagen 1A2 gene on chromosome 7,32 or the dentin sialophosphoprotein gene on chromosome 4.33 Even when a single gene is responsible for causing a specific disease, the disease in different families may be caused by different mutations in that gene. For example, more than fifty different mutations have been identified in the cathepsin C gene that causes Papillon Lefevre syndrome (www.genetics.pitt.edu/ctsc).34 Thus, comprehensively testing for some gene mutations may require sequencing of the entire gene. This is expensive, and for rare diseases the number of at-risk individuals may be too small to motivate diagnostic laboratories to develop and offer genetic testing.

While there has been spectacular success in identifying the genes responsible for Mendelian disorders,25 identifying the susceptibility genes involved in multifactorial diseases is more difficult.36 The genetic basis of many complex diseases is fundamentally different from that of simple Mendelian disorders. Genetic polymorphisms that are reported to be associated with increased risk in complex genetic diseases are common in the population, occurring in individuals who have or are at risk of the disease as well as in individuals who do not and will not develop disease. This is a critically important point; as a consequence, identification of a disease-associated allele in an individual without additional information usually provides little or no useful clinical information. Such DNA polymorphisms are not pathognomonic for disease, but are reported to be statistically associated with the disease trait when the frequency of a specific allele or genotype is reportedly greater among individuals affected with a specific disease than among unaffected individuals in the general population. (See Table 3.) The usefulness of such an association must be evaluated in light of the sensitivity and specificity of the association. Because association is measured at the group or population level, it is seldom possible to quantitate the contribution to susceptibility (disease risk) in an individual (see Figure 4). These associations are not

Figure 3. Sources of heterogeneity in single gene (Mendelian) disorders
Table 3. Comparison of general characteristics of “simple” monogenetic Mendelian disease characteristics to those of more “complex” genetic diseases

<table>
<thead>
<tr>
<th>Genetic Disease</th>
<th>Monogenetic</th>
<th>Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance pattern</td>
<td>Usually predictable pattern of Mendelian inheritance</td>
<td>Genetic pattern of inheritance usually not simple or an easily predictable pattern</td>
</tr>
<tr>
<td>Etiology</td>
<td>Single gene defect often causal</td>
<td>Multiple genes and environmental factors are causal</td>
</tr>
<tr>
<td>Gene penetrance</td>
<td>Typically very high</td>
<td>Highly variable</td>
</tr>
<tr>
<td>Genetic basis</td>
<td>Mutation, DNA change often significant/severe</td>
<td>Often functional polymorphism, DNA change can cause slight change in function of gene product</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Typically consistent, recognizable clinical phenotype, other genes and/or environmental factors can, in some cases, modify clinical expression, but are not necessary to cause disease.</td>
<td>Additional genetic and environmental factors necessary for disease phenotype. Clinical phenotype usually highly variable, and findings often occur over a continuum of expression from very mild to severe.</td>
</tr>
<tr>
<td>Environmental impact</td>
<td>Often minor</td>
<td>Can be significant, often necessary for disease manifestation</td>
</tr>
<tr>
<td>Genetic test</td>
<td>Often diagnostic</td>
<td>Not diagnostic, may permit estimate of susceptibility or prognosis</td>
</tr>
<tr>
<td>Onset</td>
<td>Often early in life, with acute developmental onset, may exhibit pleiotropy</td>
<td>Often adult, often chronic disease state</td>
</tr>
<tr>
<td>Terminology</td>
<td>Simple, monogenetic, Mendelian</td>
<td>Complex, polygenic, multifactorial, non-Mendelian</td>
</tr>
</tbody>
</table>

*Note: Inheritance pattern refers to segregation of disease phenotype in extended families or populations.*

Figure 4. Sources of variation in risk for complex disease phenotypes

*Variation in more than one gene contributes to susceptibility. The presence of specific combinations of polymorphic genes are required to push the genetic susceptibility to the disease phenotype threshold.*
pathognomonic for disease, and there is considerable controversy over the clinical validity of many reported associations. Before a reported association of a genetic polymorphism is utilized in clinical practice, its clinical validity and utility should be demonstrated. Important concepts of sensitivity and specificity must be addressed to quantify the risk of reported population associations in individuals (www4.od.nih.gov/oba/sacgt/reports/FINAL_SACGReport713700correctedpage27.htm).

Identification of meaningful genetic associations in common multifactorial diseases will require studies comprising thousands rather than the hundreds of individuals employed in most studies to date. Large datasets, adequate statistical power, and independent replication of studies will be needed if results are to be reliable.

Genetic Testing

As it is conceptually compelling and technologically feasible to identify genetic variants associated with disease phenotypes, the application of genetic testing in dentistry is likely to increase significantly. Consequently, the principles and concepts related to its integration into daily clinical dental care need to be considered. Identification of genetic variants alone does not constitute responsible genetic testing. Development of clinically helpful genetic tests and the effective integration of these into clinical practice cannot be taken for granted. Because the field of medical genetics has evolved so rapidly, regulation of some aspects of genetic testing is surprisingly lax. Considerations for genetic testing include when to test, whom to test, and interpretation of test results. The reasons for performing a genetic test need to be clear. Additionally, genetic testing often does not just concern individuals, but has ramifications for family members. Issues of confidentiality, discrimination, and access need to be considered.

Fortunately, a number of individuals representing diverse backgrounds and interests from academia, the general public, industry, and the government have been actively involved in the development, evaluation, and integration of genetic tests into public health, and an impressive body of work and associated literature already exists. Although consideration of ethical and social aspects of genetic testing is critically important, it is not discussed in this article because it is presented elsewhere (www.genome.gov).

Advances in genetic testing and research are raising concerns regarding genetic privacy. Current and proposed federal and state legislation may not provide adequate protection due to confusion over the meaning of privacy, inconsistency in the definition of genetic information, and lack of clarity regarding the role of insurers in a market-driven healthcare environment. Cleary, as technologies continue to change and the application of genetic testing expands, it is increasingly important to define and pursue measures that will ensure safe and effective genetic testing.

NIH/DOE Task Force/Professional Review/Consensus Panels

As a result of the rapid emergence of technologies to characterize DNA polymorphisms, there is little precedent for guidance in development and implementation of many genetic tests. The broad potential for clinical application as well as misuse, and the relative lack of regulation regarding genetic testing, an expert panel from academia, industry, and government met to discuss and develop principles and recommendations for the effective use of genetic testing. The National Institutes of Health and Department of Energy (NIH/DOE) Task Force on Genetic Testing (TFGT) (www.nhgri.nih.gov/Elsi/TGFT_final/1998) recognized that a genetic test encompasses more than just the laboratory test itself. Genetic testing carries broader implications, including patient identification, education, referral, and interpretation of results. Genetic evaluation is complicated by the fact that it commonly involves families, while health care delivery systems are generally directed at individuals.

Recommendations of the TFGT included three broad criteria for a new genetic test: analytical validity, clinical validity, and clinical utility. Evaluation of analytical validity (assurance that the laboratory performance of a genetic test is accurate and precise), clinical validity (the ability of the test to predict the disease phenotype), and clinical utility (the modification of the clinical phenotype associated with the use or nonuse of the test) of a genetic test is dependent upon the type of genetic disease and nature of the genetic variant. Recommendations of the TFGT are intended to help medical professionals, public health officials, and the public evaluate the safety and efficacy of genetic tests that are finding their way from research to clinical practice.
The U.S. Department of Health and Human Services (DHHS) recognizes that as the diagnostic and predictive uses of genetic testing continue to increase, the impact of these tests will affect all members of society. Because the use and ramifications of these tests are not yet fully realized, the DHHS established the Secretary’s Advisory Committee on Genetic Testing (SACGT). The SACGT has begun to assess the need for additional consideration for assuring the safety and effectiveness of genetic tests before such tests are introduced for widespread use. The SACGT is using multiple approaches to ensure input from a variety of public perspectives. The five major issues the SACGT is addressing, together with updated draft summaries of the committee’s recommendations, are available at www4.od.nih.gov/oba.20

Genetic Testing Considerations

A genetic test usually involves more than the laboratory assay itself. Depending on the type of test, the nature of the genetic disease, and the type of genetic variant tested, genetic testing may have different implications. Several excellent reviews and texts are available that provide comprehensive discussions of genetic testing considerations.19,40 Following are overviews of several of the major issues.

Purpose of Genetic Testing. The purpose of genetic testing is to provide information to improve clinical care. Genetic tests may be used to confirm a diagnosis, to determine prognosis, to help in selection of the most effective treatment option, or to help individuals and couples make reproductive decisions. To avoid confusion, permit evaluation of effectiveness, and avoid improper or ineffective test utilization, the purpose of a genetic test must be clear.

In general, tests should not be used unless the benefits of using the test outweigh its risks. Thus, use involves assessment of both safety and effectiveness. In the context of genetic tests, safety does not refer generally to the physical risk of obtaining DNA, but rather to the potential impact genetic information may have on the individual and family members. Privacy issues must be seriously considered.

As common underpinnings of genetic predisposition to chronic diseases are identified, it is possible that a genetic test performed for one condition may have implications for other conditions. For example, APOE genotyping was originally performed to evaluate cardiovascular disease risk, but has been subsequently found to be associated with increased risk for Alzheimer’s disease.45 As testing for genetic polymorphisms in a variety of genes with multiple disease conditions are performed, there is a risk that a genetic test for a relatively innocuous condition (such as periodontitis) may later be found to have implications for a more serious condition (such as cardiovascular disease). Availability of such information could have social, ethical, and legal implications, for example, in job or insurance discrimination.

Finally, delivery of test results, explanation of results, and the need for follow-up counseling need to be carefully considered if a test is planned for widespread use. Before widespread use of a genetic test is recommended, the goals of a testing program should be clearly articulated. In this way, the success and effectiveness of the test can be determined by comparing use of the test and its impact to not using the test.

Types of Genetic Tests and Intended Uses. As suggested by the TFGT, genetic testing can include any test (molecular, cytogenetic, or biochemical) providing information derived from the human genome and its expression. However, genetic testing should not be so broad that virtually all tests are covered in this definition.19 TFGT recommended that consideration be given to the magnitude of the genetic contribution to the disease and to avoid encompassing testing for genetically common conditions for which many different genes make a relatively small contribution to risk and are individually unlikely to provide clinically useful information. Most technological and economic limitations to identifying genetic variation in individuals have been overcome to the point where it is reasonable to perform such assays, or at least to envision them in the near future.39 As the laboratory technology for performing genetic testing has improved, the focus has shifted from analytic aspects of a test to defining the appropriate situations in which a test is used.

Genetic tests have many uses. They may be used as diagnostic tools, screening tools in pre-symptomatic individuals who are at risk because of family history or environmental exposure, or screening for those whose risk of disease is unknown. A genetic test may also have prognostic value. Diagnosis of the specific genetic form of muscular dystrophy affecting an individual is important in determining prognosis, for example. Determination of whether an individual has Duchenne or Becker muscular dystrophies (DMD and BMD) was historically largely dependent upon muscle biopsy for dystrophin pro-
tein assay. Now, inclusion of DNA mutation analysis in the initial evaluation of patients suspected of having DMD/BMD can provide a definitive diagnosis and potentially eliminate the need for muscle biopsy in the majority of patients. A genetic test may also be used to predict how an individual will respond to a particular drug or treatment. Knowledge of an individual’s thiorurine methyltransferase genotype can identify the risk of life-threatening myelosuppression in individuals undergoing chemotherapy with thiorurine drugs.

**Clinical Utility of Genetic Test Information.** While it is currently possible to identify the genetic variation present in individuals and to test for the presence or absence of one or more of these specific genetic variants, a meaningful interpretation of test results is not apparent in many cases, particularly for complex genetic conditions. The reason for this dilemma is that the magnitude of genetic contribution to disease may vary from negligible to complete, depending upon the disease in question. This is not to say that genetic testing is not clinically important, but clinicians must be selective and inform patients of realistic implications for positive and negative test results. The critically important concept of what is done with genetic information (post analytical phase of a genetic test) has not received proper attention in the lay press nor in the dental literature. In cases of simple Mendelian diseases, it is often possible to identify a causal genetic mutation. While this information can confirm a clinical diagnosis, it may not change available clinical treatment options, and primary prevention (at the genetic level) is generally unrealistic.

Patients must be alerted to the current limitations of genetic testing. In the case of complex diseases, it is possible to test for the presence of a specific polymorphic form of a gene (allele) that has been reported to be associated with the disease on a population level. However, the test result may be of little clinical value in terms of quantifying disease risk, modifying treatment intervention, or assessing future prognosis. For these reasons, the goals of using a genetic test should be clear. If a test provides no real diagnostic or treatment value, its clinical use should be questioned.

**Test Validation.** Genetic testing ultimately involves relating a genetically determined variant to a phenotype or biological response propensity. Two general aspects of genetic tests require validation: analytical validity and clinical/scientific validity. When performed in high-quality laboratories, genetic tests are highly sensitive and specific in detecting the variants they are designed to detect.

Currently, most regulation of genetic tests relates to analytical validation. However, an analytically very sensitive test may have high to low clinical sensitivity. For many simple genetic conditions, identification of a genetic mutation may provide for an analytically and clinically valid genetic test. However, even in the case of a simple Mendelian condition, an analytically very sensitive test may have poor clinical sensitivity because mutations in a gene that is the primary determinant of a disease may be of many different types, and not all may have been identified (e.g., cathepsin C mutations in Papillon-Lefevre syndrome or cystic fibrosis transmembrane conductance regulator mutations in cystic fibrosis). Genetic heterogeneity—in which a clinical phenotype may be caused by mutation of one of several different genes, not all of which have been identified—may also limit clinical sensitivity. Other confounding variables include conditions where the expression of a particular mutation may be impacted by other genes (modifiers), which may alter the risk of occurrence of disease in a mutation carrier or alter age at onset or disease severity. The range of phenotypes in individuals carrying identical mutations can be broad (variable expressivity). For a complex genetic condition, an analytically very sensitive test may have poor clinical sensitivity because multiple genes may act to cause a phenotype (polygenic) or may require an environmental (multifactorial) interaction to be expressed in an individual. The effect of a single gene on a complex disease trait is difficult to quantitate, and it is difficult to measure the contribution of a genetic variant to disease risk in an individual.

Although clinical utility has been demonstrated for few complex diseases, in increasing numbers, genetic tests are being proposed for genetically complex conditions before studies of clinical validity exist. Most diseases that affect significant proportions of the population are genetically complex, with multiple genetic and environmental components contributing to susceptibility. Numerous studies have evaluated the association between many different SNPs and a variety of different diseases. An extensive review of such association studies found that over six hundred positive associations between common DNA variants and diseases (including breast cancer, cardiovascular disease, pancreatitis, cleft lip/palate, and Alzheimer’s) have been reported.
associations, if real, could have tremendous implications and clinical applications for many common diseases. However, most reported associations are not robust, and the majority of reported associations of disease with a DNA polymorphism have not been consistently reproduced. This irreproducibility emphasizes the need for caution in drawing general conclusions from a single report of an association between a genetic variant and disease susceptibility.37

Clinical Validity and Utility. To establish the clinical validity of genetic tests, data must be collected under investigative protocols. In assessing clinical validation of a genetic test, it is also important that requisite data is collected from subjects representative of the population for whom the test is intended. Once a clinically valid genetic test exists for a condition, the clinical utility of the test must be evaluated. Given that thousands of genetic conditions have been identified, most of which are very rare, it is unlikely that regulatory bodies will have sufficient expertise or interest to assess every disease-causing mutation or disease-associated polymorphism. Rather, standards will need to be developed for the scientific and clinical criteria that must be met for a mutation to be considered disease-causing for a disease and for a polymorphism to be considered to contribute significantly to a disease state to be worth testing for. Clinical utility will ultimately be determined by many factors, including accepted clinical practice, cost-benefit analyses of the information gained, and its contribution to management of the condition. Cost-benefit analyses are a moving target as rapid changes in technology reduce costs for testing, and earlier intervention, when it exists, can change treatment cost.

Formal validation for each intended use of a genetic test is needed, including assessment of clinical sensitivity, specificity, and predictive value. Before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results.

Current Regulatory Environment

As a result of several factors, regulation of genetic testing is not as comprehensive as most people believe. In part this is due to the rapid advance in technology and understanding that has characterized the field in the last decade. Additionally, certain clinical practice aspects of genetics testing are inherently difficult to effectively regulate. Arguably the greatest potential deficiencies in genetic testing will arise for testing of complex traits. While analytical validity of such tests may be expected to be robust, demonstration of clinical validity will be difficult. To market a genetic test, clinical utility does not need to be rigorously demonstrated. Given the significant costs (and potential for profit) and relative lack of regulation, clinicians must consider the clinical validity and utility of genetic tests fully before incorporating them into practice. In terms of regulation, analytical and clinical validity of genetic tests are independent of one another.

Two organizations do regulate aspects of genetic testing, the FDA and CLIA. Under the Clinical Laboratory Improvement Amendments (CLIA) of 1988, analytical validity must be established for any new test put into service after September 1993. Thus, many genetic tests for dental and oral health will come under CLIA ‘88. Demonstration of scientific and clinical validity is not required under CLIA ‘88. The Food and Drug Administration (FDA) has a limited role in overseeing genetic testing. Its role primarily relates to regulation of products for genetic testing such as kits intended for use in offices or at home. Few tests have been kit-based, particularly for heritable disease testing. Tests may move towards kit-based systems, and the FDA’s role may expand. For such products, more comprehensive FDA regulations may apply which, in addition to regulation of analytical validation of genetic tests, also involves aspects of scientific validity and clinical utility.

Whereas the FDA provides oversight of manufactured kit-based tests, CLIA is the lone oversight body for tests using reagents developed in laboratories. Because new genetics tests are infrequently developed as kits that might be regulated by the FDA, they are unlikely to be subjected to significant external review of scientific validity and clinical utility.30 An additional difficulty in evaluating genetic tests is that identification of genetic variants can raise laboratory questions for which no predicate test exists—other than a clinical diagnosis that would be considered a gold standard against which the new test can be compared. In many instances, it is possible that professional organizations will be actively involved in cataloguing both gene-disease relationships and mutation-disease relationships. Given the regulatory oversight of analytical aspects of genetic testing, how tests are used is an area with high potential for im-
Genetic Screening

Recent advances in molecular genetics have highlighted the potential use of genetic testing to screen for genetic diseases. While successfully performed to screen for a variety of simple genetic conditions in newborns, genetic testing has yet to be broadly applied to adult-onset chronic diseases. It is increasingly evident that a number of chronic and systemic disease states share common etiologic factors both of an environmental and host (including genetic) nature.\textsuperscript{52} Inflammation is known to play an etiologically important role in periodontitis, and studies in animals and humans suggest the nature and outcome of inflammatory response have a significant host (genetic)-based component. However, immune responses in general and inflammatory responses specifically are in many cases redundant and not specific to an initiating factor. Consequently, it is possible that common genetically determined inflammatory responses contribute to dental (e.g., periodontitis) as well as other common diseases (atherosclerosis). The lack of specificity of a single test for predicting outcome in a complex system like the inflammatory response must be recognized, and limitations of the identification of genetic variants to predict clinical outcomes on an individual basis must be acknowledged.

Incorporation of genetic screening into a comprehensive public health program that transcends individual clinical specialties may permit development of an effective framework aimed at reducing morbidity and mortality from adult-onset chronic diseases.\textsuperscript{53} However, several issues must be addressed before such tests can be recommended for population-based screening and prevention programs. These include the adequacy of the scientific evidence, the balance of risks and benefits, the need for counseling and informed consent, and the costs and resources required. Evaluation of proposals for genetic screening in context of these principles reveals that the needed evidence is often absent, particularly with respect to the predictive value of tests, efficacy of interventions, and social consequences of testing. It will be important that the goals of genetic testing be clearly defined to permit assessment of the screening tests and interventions for those who test positive, including assessment of risks and costs, policy development, and program evaluation.

Training

The availability of genetic tests to diagnose or predict disease risk and outcomes will change the way people think about disease and how they assess the options available to them. The traditional acceptance of disease may give way to demand for a more proactive avoidance strategy. Increasingly, attention will be directed to how genetic information is incorporated into medical management. Decision analysis is a quantitative approach for dealing with the uncertainties inherent in many medical decisions, including decisions about genetic testing. Decision analysis does not guarantee a good outcome, but aims to yield better overall average results by providing a framework for people to evaluate their options and minimize cognitive biases. Dentists must explore the decision analysis process, including the terms and tools commonly associated with it.\textsuperscript{54}

Inappropriate use of genetic tests could be harmful on multiple levels and potentially waste valuable health care resources. The challenge is to generate useful information to improve health care. To understand and evaluate genetic testing, genetic principles and concepts including relevant technical terminology and methodologies will need to be included in training of health care providers. In the absence of federal regulation, the burden of evaluation of specific genetic tests, particularly regarding clinical usefulness, will be determined by appropriate boards and panels, with sufficient representation to provide comprehensive evaluation. It will be particularly important to evaluate scientific and clinical validity for tests, so that only those likely to benefit the public are used. Given the significant revenue potentials, vigilance will be needed to prevent misuse of some tests. This will be important to provide appropriate care while also protecting providers as well as consumers from potential legal liabilities.
Few dental care providers have received the education necessary to rigorously evaluate the utility of complex genetic information in preventive medicine. The subject matter comprises a formidable array of molecular and cell biology, clinical medicine, statistical genetics, epidemiology, ecogenetics, and evaluation of screening and testing methods, ethics, and public policy. Consequently, the dental community is generally poorly prepared to integrate genetic testing into clinical practice. While education at multiple levels is clearly needed, existing resources need to be explored. Dentists are not the only clinicians and educators unprepared for the impact of genetics on health care.

A challenge facing the dental community is to develop appropriate discourse that will guide initiatives to incorporate genetic testing into the profession in a responsible manner. Organizations representing clinicians such as the American Dental Association, the American Dental Hygiene Association, and specialty dental organizations need to work with the American Dental Education Association and dental educators at multiple levels to foster education and to develop guidelines for the integration of genetic testing paradigms for dentistry. These groups can benefit from analyzing how other care providers, including physicians and nurses, have proceeded. Interaction with established groups such as the National Coalition for Health Professions Education in Genetics (NCHPEG),16 established by the National Human Genome Research Institute of the National Institutes of Health, will be advisable.

As genetics increasingly impacts health care, traditional methods of training and care will be challenged. Just as the field of oral medicine incorporates professionals with diverse skills and functions, the opportunity exists to develop new areas such as dental genetics counseling, perhaps by integrating dental training programs with existing clinical genetic counseling programs.

Public Health Considerations

Medical genetics and public health share a focus on populations in practice, disease, and policymaking. While the effective integration of genetics and public health services is a key to effective disease intervention, it will be essential for clinicians, consumers, and policymakers to understand the heritable issues to ensure optimal results. Understanding the functions of genes and the significance of variation in specific genes will require researchers to learn how those genes and their gene products interact with metabolic, nutritional, and behavioral factors and with exposures to various chemical, physical, and infectious agents. This understanding will be essential to fully implement the expectations outlined in Figure 1.

Successful understanding of etiological factors important in complex traits will require very large study populations and tremendous resources. Ultimately, it may require societies’ taking part in long-term studies, and for such effort they must feel ownership of part of the process. Understanding of the genetic concepts and health care issues will be essential to gain widespread participation. Education of both providers and consumers will be necessary. While formal state or federal regulation of key aspects of genetic testing is likely to increase, it is clear that effective and appropriate integration of genetic concepts and principles into the public health arena will require understanding of the issues by all.

The role of genetics in dentistry will continue to evolve in the oncoming years. We hope this paper will encourage discussion of some of the issues that must be considered by oral health providers to integrate genetic concepts and principles into clinical practice.

REFERENCES