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REVIEW ARTICLE

Personalized Medicine: Emerging as a Silver Lining in Dentistry

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ABSTRACT

Personalized medicine is a revolution in the medical or dental field as it allows prevention and treatment of diseases based on genomic technologies. Information about a patient's proteinaceous, genetic, and metabolic profile could be used to tailor medical care to that individual's needs. Stratification can be thought of as a core element of personalized medicine. Its implementation in the various fields of dentistry—for example, in severe early childhood caries, malocclusion, oncology, and temporomandibular joint disorders—has emerged as a silver lining. Understanding the disease pathways, genomic interactions, and novel biomarkers of oral conditions before the occurrence of the disease will help in preventing the disease and, to some extent, will guide treatment planning.

Keywords: Genotyping biobanks, Precision medicine, Stratification.

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INTRODUCTION

It's far more important to know what person the disease has than what disease the person has.—Hippocrates.

Numerous terminologies including "precision medicine," "stratified medicine," "targeted medicine," and "pharmacogenomics" are sometimes used interchangeably with "personalized medicine."

"Precision medicine" is perhaps most synonymous to "personalized medicine" and has been defined by the National Academy of Sciences (NAS) as "the use of genomic, epigenomic, exposure and other data to define individual patterns of disease, potentially leading to better individual treatment."

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Table 1: Various denotations for personalized medicine

- A form of oral health care that focuses on each individual's unique clinical, genetic, genomic, and environmental information. Personalized dentistry utilizes our advancing knowledge of the molecular bases behind oral disease to develop preventative health care strategies that keep individuals from ever entering a diseased state.[1]
- Personalized medicine is a medical model that uses molecular profiling technologies for tailoring the right therapeutic strategy for the right person at the right time, as well as for determining the predisposition to disease at the population level and to deliver timely and stratified prevention—World Health Organization (WHO), 2013.[8]
- Personalized medicine combines human genome, information technology, and biotechnology with nanotechnology to provide treatment based on individual variation *vs* population trends.[2,3]

"Stratification" refers to the division of patients with a particular disease into subgroups, based on a characteristic of some sort, who respond more frequently to a particular drug or, alternatively, are at decreased risk of side effects in response to a certain treatment. Stratification can be thought of as a core element of personalized medicine. "Pharmacogenomics" (PGx) – the study of variations of deoxyribonucleic acid (DNA) and ribonucleic acid characteristics in relation to drug response—is a critically important area of personalized medicine where significant progress has recently been made (Table 1).[4]

Dentists do not get much genetic training, so they do not know how to apply these genomic technologies in their clinical practice. Advances in genomic technologies will now lead researchers to find the etiology of any disease based on genes. As the methods of genomic analysis become increasingly practical for use in the clinic, there will come a point when the utilization of genomic technologies in clinical oral health care becomes unavoidable. Genomic testing could allow risk-based long-term planning for more effective dental disease prevention, reduce the uncertainty of diagnosis and prognosis, and guide the selection of drugs or treatment protocols that minimize harmful side effects to ensure a more successful outcome for patients.[1] Information about a patient's proteinaceous, genetic, and metabolic profile could be used to tailor medical care to that individual's needs.[5] The area of personalized medicine, which delivers individualized treatment based on patient's genetic and clinical characteristics, seems to bring revolution in the field of medical sciences.

BACKBONE OF PERSONALIZED MEDICINE

Personalized medicine can allow screening, and early intervention and treatment to be concentrated on those who will benefit, reducing expense and side effects for those who are not likely to benefit from effective drug interventions and treatments that are specifically designed and customized to an individual's personal genetic profile.

DIVERSITY IN GENES

There are two types of gene variation. The first is single gene variation which is variation in the single gene that is sufficient to alter the phenotype (a mutation), and the second is complex interactions which involve mutations in many genes, often with small cumulative effects, and interaction with environmental factors.[6]

Using genome sequencing technology, these groups of individuals are analyzed for the presence and absence of a finite set of specific genetic variants across the genome through genome-wide association studies (GWAS).[6]

Different types of genetic tests are done to obtain and personalize an individual's treatment. Identifying genetic risk factors for serious adverse drug reactions (ADRs) could decrease the costs of health care and improve patient outcomes.[6,7]

Understanding and identifying genetic variations ("genotyping") in drug-metabolizing enzymes has led to physicians improving the dosing of drugs for different conditions. Genetic variation also plays a crucial role in drug–drug interactions. Genotyping provides an understanding of the genetic factors that may contribute to variability in drug response and can help maximize the likelihood of efficacious treatment and minimize ADRs.[8,9]

Reduced health care costs may be achieved by individual genetic test results and/or by analyzing an individual's full genome sequence (whole genome sequencing), allowing for screening and the tailoring of drugs and treatments to minimize side effects and improve outcomes. Testing can also rule out individual disease susceptibility where there is an increased risk in the family, reducing the need for costly and sometimes invasive screening and preventative therapy. These functions all play a role in ensuring more targeted and cost-effective health care into the future.[6]

IMPLEMENTATION OF PERSONALIZED MEDICINE IN DENTISTRY

Severe Early Childhood Caries

Severe early childhood caries (SECC) is debilitating and often leads to painful abscesses, sleep deprivation, refusal to eat, and reduced stature. The multifactorial etiology of SECC involves (a) altered salivary flow or chemistry, which may result from many medications and certain diseases; (b) frequent intake of fermentable carbohydrates; and (c) enrichment of specific microorganisms. Various other factors have been associated with severe cases, and less dramatic cases with complex etiologies may not be recognized or reported. Personalized medicine goals for SECC are to identify patients early and guide more successful outcomes.

Scardovia wiggsiae is a Gram-positive bacillus found in oral cavities and thought to be a causative agent for early childhood dental caries.

In one study, two genes, TAS2R38 and TAS1R2, appear to mediate the sensation of taste. Although preliminary, the results suggest that some individuals with variations in these genes may have a gustatory predisposition to eat cariogenic foods, offering the potential to introduce genetic factors into risk-assessment algorithms that also consider health history, oral hygiene, dietary practices, and other biological and environmental risk factors.[10]

Dental Caries

Dental caries is the most prevalent disease among children. The development of dental caries is multifactorial in nature, involving interactions among genes, gene products, the oral microbial community, diet, and lifestyle. Overall, studies have estimated that 40 to 60% of caries susceptibility is genetically determined.[14] Understanding the genes that contribute to host risk and resistance to caries will aid dentists in identifying at-risk individuals who can then be provided with more frequent hygienic maintenance and a customized, more aggressive treatment plan. Mutations in specific genes have been linked to caries development. Single-nucleotide polymorphisms (SNPs) of AMELX, a gene coding for a protein crucial for normal enamel development, have been correlated with increased caries susceptibility. A study of six SNP markers found that ENAM, which codes for a protein modulator for mineral formation and crystal elongation in enamel, also affects caries susceptibility. Defects in the KLK4 gene, coding for a protein expressed during enamel maturation, cause the hardness of enamel to decrease and also increase the individual's susceptibility to caries. Genetic variations can impact caries formation in combination with the influence of environmental factors. In addition, there is now evidence that additional, unrelated, single genes are linked to caries development, including genes related to taste receptors.[14] The salivary proteome can also be used to identify the presence of specific microbial populations that are associated with higher risk of dental caries. The information obtained from saliva samples may facilitate estimating the severity

of caries formation and personalize treatment processes to target specific bacteria.[1]

Periodontitis

Periodontitis is a common oral disease known to be influenced by genetic factors. In a GWAS study, multiple susceptibility SNPs for aggressive periodontitis have been revealed on chromosome 9p21.3 noncoding region, which was subsequently confirmed by an independent group. Interestingly, several of these susceptibility SNPs are shared with coronary heart disease, suggesting that common inflammatory pathogenic mechanisms may contribute to both diseases. This approach has identified several potentially relevant genes including those involved in the nuclear factor κB complex-mediated inflammation process, consistent with previous observations on the role of inflammation in periodontitis. Another gene identified in an epidemiological study using this approach was PIK3R1, which contains SNPs previously linked to severe periodontitis. These studies suggest that combining genomic methods, epidemiological investigations, and protein association analyses may provide a more effective approach in finding susceptibility-related genes for periodontitis, and perhaps other diseases. Microarray technology may provide a more accurate and reliable method for identifying periodontal disease subtypes through the characterization of differences in gene expression profiles. Genomic microarray analysis of saliva samples may be a useful tool for identifying oral microbes and their relative abundance to assess risks of disease development and responses to therapeutic interventions. Various immune-related proteins were found in the development of periodontitis. Coupled with the characterization of a patient's microbial profile, genomic and proteomic information will lead to more informed decision-making with regard to the application of specific antibiotics, anti-inflammatory drugs, and appropriate restorative procedures.

An interesting study of 50 families with affected members presenting with aggressive Periodontal disease (PD) by Diehl et al (2003) found that 38% of variance of immunoglobulin G allotype 2 levels could be explained by genetic contribution. One meta-analysis of association studies reports association of SNPs occurring in chronic periodontitis in the interleukin (IL)-1, IL-6, VDR, and CD14 genes, although further studies are required to validate these in larger, more stringently phenotyped populations.[11]

One such example can be found by SNPs identified in the proinflammatory cytokine genes for IL-1 (including one each in IL-1A and 1L-1B), which promote periodontal progression. A further example includes SNPs occurring within the IL-1 gene cluster that have recently been implicated in both PD and hyperlipidemia. The impact of IL-1 SNPs on two distinct pathological conditions is simultaneously amplified by both increasing risk for myocardial infarction and promoting diabetes pathogenesis.[11]

Head and Neck Cancer

Head and neck cancer, also known as head and neck squamous cell carcinoma (HNSCC), is a group of cancer types developing from the mucosal cells within the upper digestive tract. Similar to caries and periodontal disease, the development of HNSCCs is associated with the progressive accumulation of numerous gene mutations through interaction with other genes and the environment. Mutations in the genes ADH3, CYP1A1, GSTM1, GSTT1, and UGT1A7, which encode alcohol dehydrogenase and xenobiotic-metabolizing enzymes, have been shown to increase the risk of developing tobacco-related HNSCC.[1]

If a squamous cell carcinoma is identified within the oral cavity, microarray technology can subsequently reveal the unique patterns of gene expression associated with that specific carcinoma, using this information to better understand its etiology and eventually improve the HNSCC's diagnosis, prognosis, and response to drug therapy.

The use of PM to improve treatment responses in oncology reinforces the likelihood that this approach will advance incrementally as specific applications are identified with compelling clinical utility and sufficient value to drive adoption.[12]

The detection of any cancer in its earliest stages is a key factor in improving prognosis and preventing disease progression. Microarray technologies provide the ability to identify HNSCCs through the presence of specific disease biomarkers found in biological sources other than the tumor itself.

The wider goal of modern PM is stratification of populations not just to improve treatment outcomes in existing diseases, but also to predict disease risk in healthy people and devise tailored interventions with the aim of preventing or mitigating the development of disease. While the utilization of salivary diagnostics has presented critical insights into oral squamous cell carcinoma (OSCC) detection, integration of salivary biomarker data into OSCC databases has yet to be fully achieved. It is important to continue developing salivary diagnostic technologies for preventative oral health care applications.

Oral Cancer

Oral squamous cell carcinoma accounts for about 90% of oral cancers. Genetic predisposition to OSCC has been linked to deficiencies in cell cycle control, DNA repair,

and carcinogen metabolism. For example, the SNP A/G870 in the CCND1 gene encoding for protein Cyclin D1 is associated with increased OSCC susceptibility, and a polymorphism of UGT1A1 may lead to poor metabolism of the carcinogen benzopyrene. Mechanistically, OSCC may be associated with multiple genetic alterations that modify the normal functions of proto-oncogenes and tumor suppressor genes.

Unlike conventional chemotherapy or radiation, the new, customized methods—among experts also referred to as "targeted therapy"—focus their effect specifically on points of attack that are distinctive for cancer cells.[13]

The National Cancer Institute's Early Disease Detection Network has initially validated seven salivary OSCC transcriptome biomarkers (DUSP1, H3F3A, IL1B, IL8, OAZ1, SAT, and S100P) in over 220 patients.

Acute and Chronic Orofacial Pain

Pharmacogenomics provide safer and more effective dosing of drugs for conditions such as depression, anxiety, coronary and peripheral artery disease, inflammatory bowel disease, and cancer points to exciting opportunities for the management of oral health conditions such as chronic orofacial pain. Particularly relevant to dentistry is the well-documented individual genetic variation in the cytochrome P450 superfamily of enzymes involved in the metabolism and bioactivation of about half of all drugs. For instance, people with certain allelic variants in the CYP2D6 gene are unable to convert codeine to morphine and these individuals experience insufficient analgesia. Conversely, individuals with multiple copies of CYP2D6 metabolize codeine extremely rapidly, putting them at risk for morphine intoxication. Variants in the CYP2E1 and OPRM1 genes yield inter-individual differences in response to anesthetics. Identifying and monitoring such individual genetic variation may enable dentists to customize perioperative and postoperative pain management such that it is both safer and more effective.[10]

Temporomandibular Disorders

For degenerative joint-related temporomandibular disorders (TMDs), such as osteoarthritis, biomarkers appear to help stratify patients further. This research intersects the overall effort to identify biomarkers that predict disease progression and treatment outcomes in osteoarthritis and rheumatoid arthritis. The near-term PM opportunity for TMD is in characterizing degenerative cases to improve research and refine clinical classification. Ultimately, the goal for TMD patients is to identify subsets that benefit from specific therapies.[12]

Initial results have revealed that TMD appears to be associated with alterations in autonomic function and pain perception, along with genetic factors. The findings confirmed existing associations for two genes, HTR2A and COMT, and uncovered new potential risk factors linked to NR3C1, CAMk4, CHRM2, IFRD1, and GRK5, genes known to influence stress response, psychological well-being, and inflammation. Collectively, these gene alterations may represent important markers of TMD risk and, possibly, therapeutic intervention.[10]

Malocclusion

Applying genetic knowledge to the field of orthodontics will augment the current differential diagnosis of malocclusion, permitting recognition of different types of malocclusion that are etiologically discrete and so might respond to treatment in different ways. Genetic variation of the protein Myosin (type I) contributes to mandibular prognathism. As it becomes clearer what genes are involved in excessive mandibular growth, it is highly likely that genetic analysis will contribute to our knowledge of how to manage this problem. Knowledge of the type of craniofacial growth associated with specific genetic variations could help greatly with both the type and timing of orthodontic and surgical treatment. Recently, reports of genetic alterations in the parathyroid hormone receptor 1 (PTH1R) gene further confirmed the molecular basis of tooth eruption; a mutation in the PTH1R gene results in a striking failure of eruption that is hereditary (typically observed as a posterior lateral open bite).

Keys to successful treatment outcomes include knowing how different patients respond to various treatment modalities, and how the natural history of many skeletal and connective tissue disorders impact short- and long-term orthodontic treatment outcomes. In the more distant future, linkage studies that lead to the identification of specific genetic mutations responsible for certain malocclusion will form the basis for studies that create specific drug targets to correct discrepancies in facial growth. Genetic screening tools (saliva or buccal cell) are taken as a sample is taken at the initial records visit can be used for diagnosis and to predict predispositions to iatrogenic consequences in patients.[2]

ORAL BIOMARKERS

Biomarkers are measures of "normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group 2001). They are physical, functional, or biochemical indicators with a range of potential applications to clinical practice, including baseline risk assessment, disease prognosis, and treatment guidance.

Saliva has long been recognized to have several advantages over blood as a diagnostic fluid. Biomarkers have been identified in saliva and oral tissues, including signaling pathways, enzymes, proteins, and cytokines. Despite the fact that biomarkers hold great promise for oral health care, implementation into clinical practice remains a lengthy and expensive enterprise, requiring strong and creative collaborations among scientists, clinicians, and industry.

BIOBANKS

Through personalized medicine, medical sciences are able to provide each individual patient with the right medication, at the right time and in the optimum dosage. One important basis for personalized medicine is biomarkers: Biological indicators that provide information on a person and his or her body. The first priority in medicine must be to further improve diagnostic methods in the future."[12] To do that, it is crucial to know which markers might be important for a respective tumor. As a source of patient information, tissue, urine, and stem cells are preserved in the biobanks in a deep-freeze state. Sometimes, these are stored for decades in the biobanks. A central database keeps track of the various disease stages and test results with which the samples are associated. Scientists worldwide depend on biobanks for medical progress. For instance, they hope to make new discoveries about biomarkers and their relevance for different causes of a disease. If a new biomarker is discovered, scientists can significantly accelerate research on diagnostics and therapy with the help of biobank samples and the corresponding patient data.[13,14]

INFERENCE

The most undeveloped aspect of personalized medicine is the integration of genomic information with clinical and physical examination data. Most oral, dental, and craniofacial diseases and disorders, such as dental caries, periodontal diseases, oral and pharyngeal cancers, chronic orofacial pain, and cleft lip/cleft palate, arise from a complex interaction of genetic, biological, behavioral, and environmental factors. Understanding the disease pathways, genomic interactions, and novel biomarkers of oral conditions before the occurrence of the disease will help in preventing the disease and, to some extent, will guide treatment planning. Dental schools will need to incorporate genetics and genomics into their professional curricula, and dentists will need to keep up with rapidly changing technologies – including but not limited to "omics" – to keep abreast of the modern clinical care that patients expect.

Hence, genetic knowledge has the potential to influence lifestyle choices and decisions about preventative measures as well as medical and surgical treatments to improve patient outcomes.

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