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ORIGINAL ARTICLE

# Progress in oral personalized medicine: contribution of 'omics'

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***Background***: Precision medicine (PM), representing clinically applicable personalized medicine, proactively integrates and interprets multidimensional personal health data, including clinical, 'omics', and environmental profiles, into clinical practice. Realization of PM remains in progress.

***Objective***: The focus of this review is to provide a descriptive narrative overview of: 1) the current status of oral personalized medicine; and 2) recent advances in genomics and related 'omic' and emerging research domains contributing to advancing oral-systemic PM, with special emphasis on current understanding of oral microbiomes.

***Design***: A scan of peer-reviewed literature describing oral PM or 'omic'-based research conducted on humans/data published in English within the last 5 years in journals indexed in the PubMed database was conducted using mesh search terms. An evidence-based approach was used to report on recent advances with potential to advance PM in the context of historical critical and systematic reviews to delineate current state-of-the-art technologies. Special focus was placed on oral microbiome research associated with health and disease states, emerging research domains, and technological advances, which are positioning realization of PM.

***Results***: This review summarizes: 1) evolving conceptualization of personalized medicine; 2) emerging insight into roles of oral infectious and inflammatory processes as contributors to both oral and systemic diseases; 3) community shifts in microbiota that may contribute to disease; 4) evidence pointing to new uncharacterized potential oral pathogens; 5) advances in technological approaches to 'omics' research that will accelerate PM; 6) emerging research domains that expand insights into host–microbe interaction including inter-kingdom communication, systems and network analysis, and salivaomics; and 7) advances in informatics and big data analysis capabilities to facilitate interpretation of host and microbiome-associated datasets. Furthermore, progress in clinically applicable screening assays and biomarker definition to inform clinical care are briefly explored.

***Conclusion***: Advancement of oral PM currently remains in research and discovery phases. Although substantive progress has been made in advancing the understanding of the role of microbiome dynamics in health and disease and is being leveraged to advance early efforts at clinical translation, further research is required to discern interpretable constituency patterns in the complex interactions of these microbial communities in health and disease. Advances in biotechnology and bioinformatics facilitating novel approaches to rapid analysis and interpretation of large datasets are providing new insights into oral health and disease, potentiating clinical application and advancing realization of PM within the next decade.

Keywords: *microbiota*; *precision medicine*; *'omics'*; *big data*; *biomarkers*

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Technology and bioinformatics are catalyzing evolving conceptualization of 'personalized medicine' along its path to clinical translation. Personalized medicine has evolved to embrace 'predictive medicine', and more recently, has become nearly synonymous with 'precision medicine' (PM) (1, 2). PM encompasses definition of disease susceptibility, drug response, and definition of biomarkers that can be used to screen, predict disease onset, or monitor response to therapeutic intervention. As currently envisioned, PM involves the practice of medicine in a manner that interprets specific individualized patient information to proactively guide decisions made with regard to prevention, diagnosis, and treatment of disease. PM takes into account personal health data,

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which reflect an individual's metagenomic, proteomic, and/or metabolomic profile across time. Ultimately, its achievement will revolutionize approach to the clinical practice of medicine but currently advancement remains in the research arena where considerable progress toward realization is being made.

A literature review was undertaken across the spectrum of relevant 'omics' and other emerging research domains with the goal of summarizing progress toward realization of oral PM within the next decade. The scan was undertaken to review evolving understanding of oral health using current state-of-the-art technologies and novel research in new scientific domains where advances in realizing oral PM are presently being made, supported by selected examples from recent scientific literature.

The oral microbiota collectively contribute nearly one-third of the metagenome, which encompasses both host and microbial genomic content. Because evidence-based literature support the impact of oral microbiota on both oral and systemic health, a major focus of the review centers on microbiome research and its relevance to PM.

## Present investigation

### *Approach*

A search of peer-reviewed literature describing oral 'omic'-based research or research associated with emerging research domains germane to oral health was conducted using mesh search terms. Limits included 'humans', 'English language', and publication within a time frame encompassing the past 5 years for articles published in journals indexed in the PubMed database. Using a narrative approach, recent advances were descriptively summarized citing relevant examples from the literature to support their potential for promoting realization of PM. The current literature was further reviewed in the context of historical original research and reviews, in order to delineate an overview of the current state-of-the-art technologies.

### *Results*

#### State of the art in PM

*Historical progress in personalized medicine and relevance to oral medicine.* Translation of personalized medicine from concept to clinical application is presently being realized and is most advanced in the realm of pharmacogenomics which impacts both oral and systemic medicine. Historically, pharmacogenomics first gained significant traction with the elucidation of the central role of the cytochrome p450 (CYP) superfamily of enzymes in drug metabolism which collectively contribute to the metabolism of $>90\%$ of pharmacological agents used clinically (3, 4). Identification of genetic polymorphisms in the CYP450 genes was shown to impact drug metabolism rates that manifested in four clinical phenotypes: poor, intermediate, extensive, and ultra-rapid metabolizers (5). These insights spurred intensive research efforts toward defining and characterizing inter-individual variation in drug responsiveness as an important focus for the advancement of PM.

An example of pharmacogenetic impact on oral medicine is found in adverse drug events (ADE) and lack of efficacy of drugs metabolized in the CYP2D6 pathway in a subset of patients. It is now recognized that depending on race and ethnicity and polymorphic genotype, $\geq 20\%$ of the population may be impacted by genetic polymorphisms in *CYP2D6* (6), causing individuals encoding specific polymorphisms to derive little pain relief and/or experience significant ADEs if exposed to codeine, a drug often prescribed for pain relief following oral procedures such as tooth extractions. The Clinical Pharmacogenetics Implementation Consortium has now published efficacy evaluation and dosing guidelines based on CYP2D6 phenotypes to guide use of codeine and opioid administration for pain relief. Furthermore, drug metabolism panels with good sensitivity and specificity have been developed to screen and phenotype metabolic capacity based on enzymatic genotypes [reviewed by Samer et al. (7)]. In a separate example, xerostomia (dry mouth) represents an oral ADE manifestation associated with exposure to one or more drugs and it ranks among the most common oral disease, affecting one in five individuals. Oral consequences of this condition include heightened susceptibility to periodontal disease (PD), caries, halitosis, candidiasis, dysesthesia, dysphagia, mucositis, sialadenitis among others, and systemic conditions such as Sjogren's syndrome (8).

As noted above for opioid administration, progress in genetic research related to pharmacogenetics is beginning to find its way into clinical practice. Significant efforts are currently under way to integrate the human pharmacogenetic data into electronic health records (EHRs). The electronic MEdical Records & GEnomics (eMERGE) network is one such effort that was established by the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH) in 2007 (www.emerge.mc.vanderbilt.edu/). The eMERGE network combines DNA biorepositories with EHRs for large-scale, high-throughput genetic research with the ultimate goal of returning genomic testing results to patients in a clinical care setting. The eMERGE network started with a focus on discovery using genome-wide association and have recently been involved with investigating methods to incorporate new genomic information tied into the clinical decision support into EHRs to afford better decision making by the providers at point-of-care (9). Such progress speaks to greater receptivity by practitioners in the clinical setting to engage emerging data that have, to date, been regarded as purely investigational.

Establishment of monitoring systems to detect early ADE signals through population surveillance is also



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critical to achieve PM and is therefore a noteworthy advance. Approaches include: 1) application of machine learning to detect emergence of differences in rates of potential ADEs in a drug-exposed population compared to the non-exposed general population, and 2) seeking clues regarding mechanisms inducing the drug-induced pathology (10).

*Profiling microbiomes in health and disease: evidence of constituency patterns as potential biomarkers for oral PM.* Each individual's metagenome is composed of the collective DNA contributed by each unique host and its cohabitating microbiota, which have evolved to live symbiotically with their human host. Existence of a 'healthy core microbiome' whose characterization is ongoing has been posited and is thought to contribute to this symbiotic state. The constituency of oral microbial communities varies by niche in the oral cavity and reflects health status. Constituent flora of the various discreet oral microbiomes are influenced by myriad factors in the local environment including pH, relative anaerobicity, nutrient requirements and availability, other co-constituent microorganisms and their relative concentration, salivary content, and exposure. Microbiomes are further impacted by host factors including genetics, immune status, health status of the oral cavity, age, and overall health of the host. Thus, the oral microbiome could be affected by various intrinsic and extrinsic factors. Intrinsic factors might include lack of consistent, optimum oral hygiene, genetic susceptibility to chronic oral diseases, and systemic diseases that could affect oral environment (e.g. gastric reflux). Extrinsic factors might include dietary and chewing habits, use of tobacco-related products, and medication exposures (including chemotherapy and radiation), whose ADEs may impact oral health.

Evidence increasingly suggests that pathologies arising in the oral cavity impact both oral and systemic health. Perturbations among oral microbiota that disturb the homeostatic relationships with the host and that exert secondary impacts on other systemic microbiomes are also being characterized and have accelerated efforts in the domain of metagenomics and microbiome research. This research is investigating the premise that departures from a healthy oral status allegedly tip the balance of homeostasis in a local oral microbiome in favor of organisms with pathogenic potential facilitated by shifts in the local environmental conditions. These shifts may be potentiated by underlying processes supportive of pathogenesis including mediation of direct systemic access of organisms normally limited to the oral cavity. For example, nosocomial pneumonia or ventilator-associated pneumonia may arise in hospitalized patients as a consequence of oral pathogens gaining pulmonary access, especially in the context of poor oral hygiene and oral pathology, including PD (11, 12).

*Core microbiomes.* Differences in the relative diversity of microbiome organization across various oral niches, including tooth surface, gingival sulcus along its depths, tongue, saliva, cheeks, palates (soft and hard), and tonsils, have been demonstrated. Progress in defining 'healthy' core microbiomes in the context of distinct oral niches has included characterization of specific phyla and taxa whose prevalence may vary across individuals. A recent review by Chen and Jiang (13) summarized how sequencing approaches, including pyrosequencing, sequencing by synthesis, or ligation, have contributed to defining relative diversity in oral microbiota profiles in health and disease states, including cariogenesis and PD. These authors concluded that cumulative evidence increasingly supports existence of a core oral microbiome (14–21) and have begun to define the microbiota associated with health and disease and changes noted across the spectrum of aging. For example, Aas et al. (20) undertook definition of normal bacterial flora in the oral cavity of healthy individuals sampling nine oral niches. The authors reported predominance of 141 species, of which 60% have not been cultured, identified 13 new phylotypes, and noted absence of traditional pathogens associated with PD and cariogenesis in the healthy individuals (20).

An emerging theme noted in many studies evaluating microbiome constituency is that differences in relative balance of constituent populations either align the host with health or predispose to disease development. Microbiome characterization has revealed the presence of more than 700 species in the oral cavity alone, representing nearly one-third of the estimated 3,000 microbes represented in the systemic metagenome. To date, over 60% have been identified only by culture-independent molecular approaches and some appear to represent pathogens. Thus, more than half of the constituent microorganisms identified in the oral cavity to date remain largely uncharacterized, and their relative contribution to oral and systemic disease remains to be defined (22).

While the concept of 'healthy core microbiome' has gained traction, it remains to be defined from a global population perspective, since it may vary across populations. Ideally, characterization and comparisons of healthy populations worldwide inclusive of different race ethnicities, variability in diet and nutrition, hygiene and sanitation practices are required to distinguish patterns. Several studies have recently begun to examine the impact of hereditary and environmental factors (23, 24).

*Characterization of the cariogenic-predisposing microbiome.* Ling et al. (25) profiled the presence of approximately ten bacterial phyla, six of which exhibited significant variability in relative abundance in plaque depending on oral health status relative to cariogenic status, including *Streptococcus*, *Veillonella*, *Actinomyces, Granulicatella, Leptotrichia*, and *Thimonas*. The latter three phyla were

present in highest abundance in the context of severe cariogenesis in early childhood, while *Aestuariimicrobium* was more abundantly represented in caries-free individuals (25). An analysis of a Chinese pediatric population reported the presence of 13 genera at higher levels in healthy children without caries compared to those with caries (16). The authors postulated that shifts in the relative representation of phyla and genera, rather than the presence of specific pathogens, may be central to establishment of a caries-inductive environment. At the genus level, up to 15 genera have been reported in healthy subjects, with *Streptococcus*, *Haemophilus*, *Neisseria*, *Prevotella*, *Veillonella*, and *Rothia* representing the most abundant genera, while inter-individual variability in their dominance was noted (21).

*Characterizing microbiome constituency in PD.* In the context of PD, a recent study by Lourenco et al. (26) concluded that 'microbial signatures' were distinguishable within microbiomes of individuals with and without PD, and these were distinct from profiles seen in aggressive PD. A study by Griffen et al. (27) reported higher microbial diversity in association with PD compared to subjects with no disease, with 123 species versus 53 species identified, respectively.

*The diabetic microbiome.* Notably, host response to disturbances in homeostatic balances in host microbiomes includes upregulation of inflammatory processes with local and systemic impact (28). Type 2 diabetes mellitus (T2DM) provides a salient example. Evidence suggests that the gut microbiome is a determinant of body weight, adiposity, intestinal permeability, and insulin production (29). This suggests that the microbiomes may play a significant role in the development of obesity and T2DM, two linked pathologies that exhibit an epidemiological progression. Moreover, T2DM and PD are frequently associated with bidirectional exacerbation, such that PD has been designated as a complication of T2DM (30, 31). Mechanistically, this relationship is presumably mediated by heightened inflammatory processes, resulting in significantly increased risk for PD and alveolar bone loss (32–34). Five systematic reviews support validity of this relationship based on studies demonstrating improved glycemic control with attenuation of periodontal inflammation following treatment (35–39).

Microbiome profiling in subjects with T2DM suggests that affected individuals may have distinctive profiles. A study by Casarin et al. (40) characterizing subjects with uncontrolled T2DM and chronic PD noted that *Fusobacterium nucleatum*, *Veillonella parvula*, *V. dispar*, and *Eikenella corrodens* were significantly more predominant in diabetic subjects than in non-diabetic subjects and further suggested that diabetic status impacted on the burden and diversity of bacteria relative to PD status. Zhou et al. (41) showed that *Porphyromonas gingivalis*, *Treponema medium*, *Tannerella forsythia*, *Porphyromonas endodontalis*, *Filifactor alocis*, and *Leptotrichia* spp. are significantly associated with PD in subjects with T2DM, while *Selenomonas sputigena* was associated with non-diabetic subjects.

*Advances in defining clinically informative biomarkers of oral/systemic health: salivaomics.* Saliva has been found to be a reservoir of biomarkers that reflect oral and systemic health status. Because it is a readily accessible body fluid that can be cost-effectively collected, initial progress has been made in the development of saliva-based assays with potential for clinical application in the domain of salivaomics, which encompasses salivary proteomics, transcriptomics and regulatory elements (e.g. miRNA), metabolomics, and the microbiome (42). While not yet poised for adoption into standard clinical care, current efforts predict the potential for expanded integration of molecular analysis into clinical care and decision support on a personalized basis. Wei and Wong (43) and Giannobile et al. (44) provide compelling overviews of requirements and challenges that are currently being defined and addressed as efforts to incorporate saliva-based diagnostics at point-of-care are being explored in the dental arena, including practitioner receptivity. Such tools hold great potential for predicting response to therapy and as diagnostic tools.

In the realm of translating insights regarding constituency of microbiomes in health and disease, use of saliva offers a potential medium to study microbial signatures of organisms present in the oral cavity or estimate their relative abundance and potential contribution to specific oral diseases. Yang et al. (45) developed HuMIChip microarray to profile functional genetic signatures of oral microbes present in saliva of individuals with and without caries. Whereas diversity and quantitative indices were similar, network analysis identified greater divergence in 'non-core' genes and retention of the integrity of core genes. The authors concluded that functional gene signature of salivary microbiota in healthy subjects was distinct from that of subjects with caries. Functional gene signatures detected in caries-associated saliva aligned with enzymes with potential for caries promotion (45). At a systemic level, the salivary microbiome profiles have been associated with systemic disease. For example, the salivary microbiome profiles exhibited 94% sensitivity and 82% specificity in distinguishing patients with early-stage, resectable pancreatic cancer based on shifts in the microbial signature, with *Neisseria elongata* and *Streptococcus mitis* emerging as specific biomarkers, whereas *Granulicatella adiacens* and *S. mitis* were associated with chronic pancreatitis (46).

Other studies have also linked *P. gingivalis* to pancreatic cancer (47), and carcinogenic links to oral bacteria are being increasingly described. Oral squamous cell carcinoma has been associated with dysbiosis of the mucosal



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microbiome and markedly increased levels of *P. gingivalis* and *F. nucleatum* (48). Genomic analysis has further demonstrated association of *F. nucleatum* with colorectal cancer (49). Utility of microbiome analysis in cancer screening will require further study and validation in larger, diverse patient cohorts.

Additional progress has also been made in characterizing salivary proteomics, with 1,166 proteins currently defined, while transcriptomic research has revealed a core of 180 mRNAs present in saliva. Furthermore, miRNAs, which regulate gene expression largely through mRNA regulation, are proving to be potentially useful biomarkers in the context of evaluating gingival health. For example, Lee et al. (50) demonstrated that six of eight miRNAs known to be associated with inflammatory processes are upregulated in gingival tissue of subjects with chronic PD.

*Epigenetic biomarkers.* Based on emerging evidence, Grover et al. (51) have postulated further roles for epigenetics in association with PD. These investigators proposed that: 1) pathogen emergence may be supported by host cell alterations arising as a consequence of epigenetic alteration, or alternatively, 2) occurrence of epigenetic alteration stimulated by environmental factors or microbial factors support establishment of dysbiosis (51). For example, Andia et al. (52) noted hypomethylated stretches in the IL-8 proinflammatory cytokine gene promotor in subjects with aggressive PD compared to controls, suggesting that hyperinflammatory responses and resulting tissue damage may contribute to establishment and maintenance of dysbiosis. A further example includes the observation by Yin and Chung (53) of hypomethylation of a zinc finger gene in gingival epithelial cells in the presence of *P. gingivalis.* These authors point out that previous research demonstrated that the same zinc finger gene is upregulated in cardiovascular hypertrophy (54), suggesting that microbial stimulus associated with infectious processes might offer a possible connection between PD and processes predisposing to advancement of cardiovascular disease. Similarly, variable secretion of IL8 by gingival epithelial cells was noted on exposure of the cells to *P. gingivalis* and *F. nucleatum.* Interestingly, pretreatment with DNA methyltransferase 1 inhibitor abrogated the observed variability in IL8 secretion, suggesting a role for cellular acetylation status (53). As epigenetic therapies evolve, this research domain will deserve more attention in the future.

*How advances in informatics capability contribute to realization of PM.* Importantly, an ever-expanding framework of invaluable, freely accessible, open-source, interactive databases, and informatics tools has been created to support access to 'omic data'. As an example, great inroads have been made facilitating predictive medicine in the salivaomic research domain. This includes the creation of: 1) Salivaomic Knowledge Base (SKB), a web-based data management system; 2) SALO, a salivary ontology integrated within the Open Biomedical Ontologies Foundry (www.obofoundry.org); 3) BioMart, an open-source database system that can integrate independent databases through its BioMart Central portal, providing facile adaptability to relational database management systems; and 4) SDx Mart in BioMart, where proteomic, metabolomics, and transcriptomic data can be interfaced and integrated to support biomarker exploration (42). The advent of such public resources will accelerate progress in PM by linking myriad data sources that facilitate exploration of how omics research discoveries mesh at a molecular level and how understanding of these relationships can be translated into clinical care. Similarly, the ability to define and compare oral and systemic microbiota will be of importance in delineating how microflora and pathogens associated with specific anatomical niches may impact disease processes in the oral cavity and systemically. Important resources are being created to support delineation of the role of the oral microbiomes to health and disease. Among them are: 1) the Human Oral Microbiome Database (HOMD, www.homd.org), a highly curated registry containing 688 oral species/phylotypes based on full-length 16S rRNA gene sequences, with more than 440 ( $\sim$65%) of these taxa now successfully cultured and with fully sequenced genomes available for 347 of them (22); 2) Core human Oral Microbiome Database (CORE, www.microbiome.osu.edu), a repository for phyloxgenetically curated 16S rDNA sequences (55); 3) the Silva database (www.arb-silva.de) 16s rRNA gene reference resources for the human oral microbiome (56) and Ribosomal Database Project Classifier, an analytical tool supporting classification through the genus level (57); and 4) OralCard (www.bioinformatics.ua.pt/oralcard), a comprehensive compilation of the oral proteome contributed by host and microbiota (58).

*Emerging research domains, systems analysis, and oral PM.* The future of oral PM lies in the capability of those in the dental arena to embrace a paradigm shift from a world view that oral disease is attributable to a limited number of known pathogens to one that visualizes disease emergence as a consequence of subtle shifts in status and constituency of the collective microbiomes and their host. This will require a systems approach to gain better insights into the nuances of interaction between the host and its vast population of microbial guests.

As examples, a study by Zdziarski et al. (59) on host imprinting on the microbial genomes demonstrated rapid and divergent evolution among individual patients with a clear pattern of adaptive bacterial evolution driven by the physiological environment dictated by the individual host. Moreover, microbiome establishment in the healthy host was associated with loss-of-gene function supporting

virulence in favor of gene expression favoring symbiotic adaptation (59). Using a systems biology approach, Duran-Pinedo et al. (60) recently undertook a simultaneous metagenomic and metatranscriptomic analysis on subgingival plaque samples collected from subjects with healthy gingiva or with PD, either from a single crevice or pooled samples collected at several sites in the mouth of the same individual, in order to characterize the functional impact of microbial gene expression patterns in health and disease. In the context of PD emergence, these authors noted that the microbiomic community collectively exhibited upregulated gene expression profiles that supported virulence factor production, thereby facilitating pathogenic processes irrespective of their classification as traditional putative periodontal pathogens or microbiota associated with periodontal health or relative representation. Functionalities enabled included lipid biosynthesis, microbial motility and chemotactic properties, upregulation of metabolic processes promoting energy metabolism, stress response, and iron transport, among others. These data support the conceptualization of Relman (61) that PD emergence is orchestrated collaboratively by the microbial community in the context of shifting constituency of the microbiome through pathogen enablement and a permissive environment. Interestingly, Duran-Pinedo et al. (60) reported absence of viral sequences among the metagenome and meta-transcriptome data. However, as an emergent domain, other viromic studies have detected various salivary bacterial viruses (mainly phages) variably present in the human oral cavity and these may also impact on microbiomic constituency and virulence (62, 63).

*Emerging research domains and relevance to oral PM.* Another fairly new scientific domain characterizing interkingdom communication posits that bacteria practice 'quorum sensing and signaling' with each other through generation of hormone-like molecules that modulate genetic expression and may impact on host cell signal transduction. Similarly, host hormones can effectively modulate bacterial gene expression through finely tuned molecular sensors. With changes in the health status of the host, microbes ideally poised to activate virulence genes will emerge based on environmental signals received (64, 65). Such an expanded view of 'oral pathogen' necessitates new conceptualization of clinical approaches to the management of oral health.

Advances in the burgeoning domain of Big Data are critical to the next phase of advancing PM. In the future, systems approaches to integrating and interpreting omics data will be necessary to fully harness the wealth of information that is being generated at unprecedented rates. Big Data toolsets such as SeqHBase (www.seqhbase.omicspace.org) with the capacity to analyze whole genome or exome sequencing data of 10 individuals in approximately 1 minute are being created and are essential to advancement of the field of PM. Eventually, analysis in multiple dimensions across distinct omic domains will enable efficient sorting of molecular data in multiple domains. The reader is referred to reviews by Weng et al. (66), Yoo et al. (67), Potamia et al. (68), and Yan (69) for summary overviews of some additional promising examples of advances in Big Data analysis and novel bioinformatics approaches that facilitate analysis of high-throughput data, clinical interpretability, and systems analysis. An overview of some of the domains that will need to be multi-dimensionally integrated to apply systems analyses is provided in Fig. 1.

Although realization of oral PM currently remains in developmental stages, oral medicine is making quantum leaps and stands well positioned for greater advances in the future through focused research in each of these domains. Datasets generated through these approaches will be available for systems and network analyses. Such studies are already in progress, revealing remarkable new insights. An example is found in a study by Belda-Ferre et al. (70) that applied functional microbiome analysis. These investigators reported pivotal findings in several functional categories in individuals without dental caries, including genes for antimicrobial and quorum-sensing peptides. Notably, *S. mutans* was not represented among colonizing organisms, and colonizers were molecularly equipped to inhibit its establishment. The authors proposed that such commensal strains might be harnessed as 'probiotics' in preventing cariogenesis (71).

## Conclusion

*Progress and challenges impacting oral PM.* While PM still largely remains in exploratory stages, considerable progress has been made in advancing technologies for delineating the complex symbiotic relationships contributing to health and disease as a prerequisite to translating PM into the mainstream of clinical care. These new technologies are generating an unprecedented volume of coded data related to physiological processes and launched the new domain of Big Data in the field of informatics to meet the challenge of identifying artifact, sorting, and interpreting these data accurately. As patterns in coded data are deciphered and interpreted, they hold potential to be monitored as biomarkers to ascertain relative health and pathological risk. The potential for realization of PM is advanced by the ability of these technologies to discern and report on biomarker status. Currently, salivaomics has made the greatest inroads in developing assays with potential for future clinical applications.

Despite much interest in microbiome research and compelling evidence that it plays a role in oral and systemic health, this discipline is still evolving. Many of the observations on how microbiomes modulate systemic health need to be replicated by independent investigators



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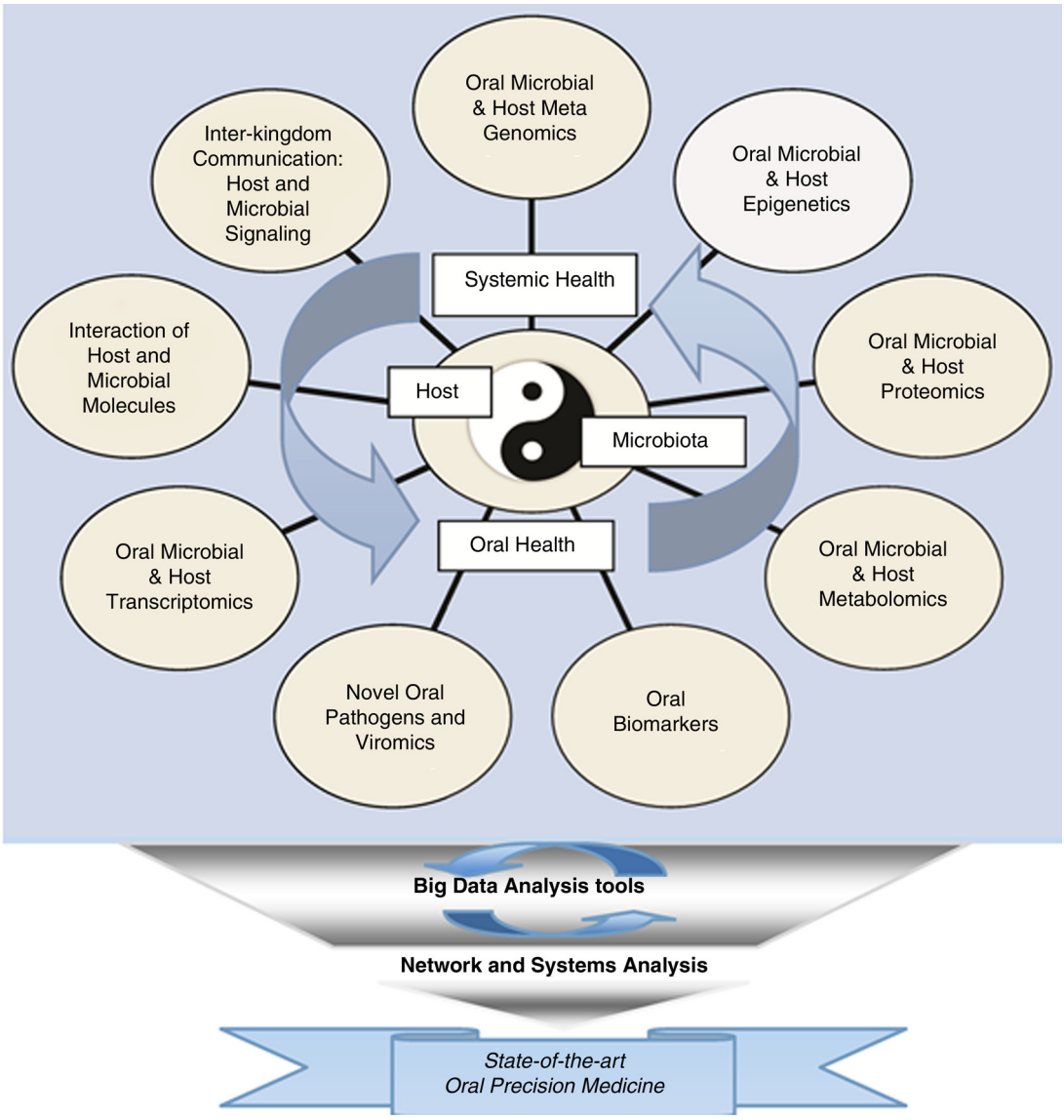


*Fig. 1.* The schematic provides a broad encompassing overview of study domains contributing to advancement of personalized medicine and deeper understanding of host–microbiome interactions. Ultimately, achieving personalized, precision oral medicine will target maintenance of oral environments that support positive symbiotic relationships between the host and oral microbiota, while minimizing deleterious impacts on systemic health associated with poor oral health.

in larger cohorts and mechanistically explained. Current comparative studies that describe the preponderance of one phylum over the other in a disease condition are of limited significance, as they are unable to distinguish if all or only some species in a phylum are pathogenic. More species-level description of bacteria associated with a disease condition and their absence in the healthy condition is needed. Little is known about the physiology, metabolic pathways, and antibiotic susceptibilities of bacteria whose presence in the oral environment has only been identified to date by 16S rDNA analysis. Thus, there is little knowledge about specific measures required to keep them in homoeostasis, and further research to characterize these organisms is needed to discern their relative contribution to health and disease. In addition, coordinated efforts are being initiated to cultivate as many of the uncultivable oral microorganism as possible to facilitate more complete phenotypic and genotypic analysis and response to treatment.

Although microbiome characterization is not likely to have immediate clinical applicability in the near future, it has been transformative in mediating a paradigm shift in conceptualization of periodontal and cariogenic pathogenesis arising from a limited number of pivotal causal pathogens to the dawning realization that microbial communities finely attuned to their environment and host, determine the balance between health and disease *via* collective relational interactions. For example, Wade (71) posits

that functional classification of microbiome constituents, which demonstrate functional redundancy, may be more informative than phylogenetic classification from a clinical perspective if probiotics can be harnessed to establish microbiomic profiles that favor health.

In the context of other technological advances described below, oral medicine is now entering the arena of network and systems analysis, which is supporting such alternative classification of disease entities. This burgeoning knowledge will make it possible to rethink therapeutic approaches based on definitions of microbial profile patterns that are currently under investigation. In the future, as clinical utility and cost effectiveness are achieved, microbiome profiling has high potential for applicability to PM.

While evidence supports a role for oral pathology in systemic disease exacerbation, a recent systematic review by Linden et al. (72) points to challenges in interpreting the existing body of research examining the relative contribution of oral disease to systemic disease risk. Historical studies are confounded by factors including variable definitions of PD (causing their elimination from analysis because they failed to meet clinical or radiographic threshold criteria validating the presence of PD), limited number of PD assessments over time, small sample size among study populations, potential bias in selection of control populations, presence of underlying comorbid disease associations, the impact of which are challenging to uncouple (e.g. diabetes and chronic kidney disease), or presence of additional confounders that are challenging to control, among others (72). However, based on the existing evidence from cross-sectional or prospective studies where threshold definitions of PD were met, potential support for association includes obesity as a risk factor for PD (73), PD as a risk factor for oro-digestive and pancreatic cancers (74), chronic renal disease (75), cognitive impairment and Alzheimer's disease progression (76), and metabolic syndrome (77). In contrast, more evidence supporting positive associations between rheumatoid arthritis and chronic obstructive pulmonary disease is needed (72). Data interpretation is further confounded by quality of systematic reviews (78). Thus, more carefully designed studies are needed. Notably, more robust data in support of positive associations between PD and cardiovascular disease, T2DM, and preterm labor have been reported in systematic reviews or evidence-based studies and have demonstrated improved systemic outcomes in response to periodontal treatment (79, 80).

Gulati et al. (80) have proposed the emergence of periodontal medicine as a domain of PM based on a growing body of evidence suggesting bidirectional consequences related to chronic infectious processes and heightened local and systemic inflammatory states that exacerbate conditions promoted by upregulation of stress-response molecules. For the near future, however, advancement of PM may consider the compelling argument of Otomo-Corgel et al. (81) that despite the current lack of consensus in the literature regarding potential associations between PD and various systemic conditions, it is important to recognize that periodontal and overall oral health is largely achievable in most individuals by prevention, vigilance, and relatively cost-effective treatment of any emergent disease, thereby further delimiting focal and systemic infectious and inflammatory processes where bi-directionality is posited (80). Thus, applied PM strategies should intrinsically seek to embrace proactive monitoring of oral health as an aspect of overall healthcare.

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