



A Perspective: Integrating Dental and Medical Research Improves Overall Health

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The past decade has seen marked increases in research findings identifying oral-systemic links. Yet, much of dental research remains poorly integrated with mainstream biomedical research. The historic separation of dentistry from medicine has led to siloed approaches in education, research and practice, ultimately depriving patients, providers, and policy makers of findings that could benefit overall health and well-being. These omissions amount to lost opportunities for risk assessment, diagnosis, early intervention and prevention of disease, increasing cost and contributing to a fragmented and inefficient healthcare delivery system. This perspective provides examples where fostering interprofessional research collaborations has advanced scientific understanding and yielded clinical benefits. In contrast are examples where failure to include dental research findings has limited progress and led to adverse health outcomes. The impetus to overcome the dental-medical research divide gains further urgency today in light of the coronavirus pandemic where contributions that dental research can make to understanding the pathophysiology of the SARS-CoV-2 virus and in diagnosing and preventing infection are described. Eliminating the research divide will require collaborative and trans-disciplinary research to ensure incorporation of dental research findings in broad areas of biomedical research. Enhanced communication, including interoperable dental/medical electronic health records and educational efforts will be needed so that the public, health care providers, researchers, professional schools, organizations, and policymakers can fully utilize oral health scientific information to meet the overall health needs of the public.

Keywords: medical-dental integration, oral-systemic research, clinical trials, interoperable electronic health records, microbiome

INTRODUCTION

Biomedical research grew dramatically after World War II with the generation of new antibiotics, the unraveling of the genetic code, the birth of molecular biology, and the first successful organ transplants, among major milestones. The National Institutes of Health (NIH) expanded accordingly, but in ways reflecting traditional clinical specialties that divide the body into disparate organs and systems, a division that perpetuates the sharp divide between dentistry and medicine.

But the very discoveries and technologies that are rapidly transforming our understanding of life and life processes demand we put the body back together again (Table 1). For example, we know that a gene associated with a particular organ can manifest in other organs, or turn other genes on or off, and we know that a drug targeted to a particular pathogen can wreak havoc elsewhere in the body. But what is also now clear is that the body is even more extensively and deeply connected than had been thought. The coronavirus pandemic is a case in point. A member of a family of viruses typically associated with respiratory symptoms, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the coronavirus disease 2019 (COVID-19), can result in fatigue, loss of smell and taste, gastrointestinal problems, cognitive deficits, depression, life-threatening pneumonia, neurological disorders and symptoms that can persist in some individuals long after initial infection (15–18). Yet the mouth and oral health considerations continue to be treated as a class by themselves, separate from the rest of the body, ignored and omitted from research studies large and small. This gap results in missed opportunities to reveal important oral-systemic interactions or explain how other parts of the body regulate functions in the mouth. This perspective provides examples of the consequences resulting from the lack of integration and the benefits gained when oral-systemic integration is in place. This is a perspective, not a review, but we provide additional references to a few scientific papers and reviews within the last 6 years, which expand on the examples provided here (19–27).

THE FAILURE TO CONNECT

Not Really All Parts of Us, but Getting Close

The goal of this innovative Precision Medicine initiative, launched by the NIH in 2015, named *All of Us*, is to build one of the most diverse health databases in history by inviting one million Americans, 18 and older, of all backgrounds, to voluntarily submit biologic samples and personal information to enable investigators to learn how biology, lifestyle and environment affect health (28). Participants are asked to answer surveys; they can submit data from wearable measuring devices and allow researchers access to their electronic health records (29). Early on, to get the program going, they were not able to include dental questions in the survey. More recently, two dental questions were added i.e., have you seen a dentist in the last 12 months and do you have access to dental care, with plans to include a more comprehensive oral-dental history, plus collecting salivary samples within the coming year, behind schedule due to the pandemic. We are optimistic that oral-dental health data will be included within the context of total health. On another positive note, UK Biobank now includes collecting salivary samples along with an oral health survey (30).

Incompatible EHRs

The goal of integrated oral and overall health data from *All of Us* is exacerbated by the general lack of interoperability between medical and dental electronic health records making it difficult to obtain an individual's inclusive dental and medical history.

Exclusion of oral health data can delay diagnoses and treatment by missing characteristic oral signs of particular conditions, syndromes and diseases, with repercussions on overall health over the lifetime. Establishing a fully integrated dental-medical electronic health record must be a priority to ensure research advances provide optimal clinical care and guidance (28, 29). We recognize the current siloed approaches are on both the medical and dental side. Many dental communities have not fully embraced interprofessional models of teaching and clinical practice, favoring the technical aspects of dentistry. We need buy-in from all healthcare teams to be successful in delivering the concepts discussed in this perspective.

Childhood Caries Risk

Failure to include oral health in other large genomic-phenomic studies also limits understanding of oral conditions directly. For example, childhood dental caries remains the number one chronic disease in children, more prevalent than asthma (30). This state of affairs is amplified by health disparities that disproportionately affect poorer groups, minorities and other underserved and vulnerable populations who lack access to care (31). While some progress has been made toward identifying genetic contributions to periodontal disease and caries (2), failure to include oral health research in large-scale genomic-phenomic initiatives of gene-environment interactions impedes mechanistic understanding of caries risk in children.

Oral Health in Aging

Biological aging is considered a normal physiological process known to be influenced by an individual's risk to include, but not limited to, hormonal changes, chronic inflammatory diseases, diet (nutrition/sugar intake/alcohol), and smoking. There is increasing evidence that periodontal disease, as a chronic infection with persistent inflammation locally and systemically, may contribute to unhealthy aging (32–35). The increasing evidence that severity of periodontal disease has a negative effect on telomere length, where decrease in telomere length is a measure of biological aging, highlights the importance of including oral health status as part of determination of one's total health across a life span (36). Another area needing attention relates to salivary flow with aging. Studies have demonstrated that even though there is some decrease in salivation and a change in salivary composition with aging, it is adequate in healthy aging individuals (37, 38). However, the onset of systemic diseases and the addition of many commonly used drugs as well as radiation therapies can irritate oral tissues and directly cause xerostomia, raising the risk of caries. Yet, how many providers recognize these risks or ask their patients if their various therapies or drug regimens have had any effects on their oral/dental tissues? The inclusion of oral health in aging research is critical to better serve older individuals and develop therapies to preserve oral health.

THE NEED FOR DENTAL SCIENTISTS IN CLINICAL TRIALS

The knowledge dental scientists bring to characteristics of oral tissues can provide valuable clues in diagnosing systemic diseases as well as predicting and elucidating the impact of new therapies

TABLE 1 | Tools and technologies informing clinical practice and oral health outcomes.

Artificial Intelligence and Machine Learning: New technologies are being applied to craniofacial disease detection, including advanced imaging and the use of artificial intelligence/machine learning. The exciting area of facial recognition has exploded with the common use of personal smart phones, security cameras, and social media. These technologies are being applied for identifying rare and undiagnosed diseases that have a craniofacial phenotype. The ability to link a 3D graphic phenotype to a mutation variant is only possible with ongoing research in quantitative imaging modalities and large-scale application to genetic data, such as the efforts of Face2Gene¹. Importantly, and with growing attention, is the need to establish careful guidelines for appropriate use of A.I. and machine learning, where improvements made in patient care do not compromise an individual's privacy (1, 2). Further, dental educators need to incorporate information in their curricula to ensure graduates are prepared to execute these and other emerging tools and technologies.

Imaging Advancements: The increasing use of cone-beam computed tomography, particularly by oral and maxillofacial surgeons and orthodontists, for evaluation of craniofacial growth, skeletal malocclusions and placement of dental implants has added an important tool to the expanding technology for research. The development of 3D craniofacial landmarks (3), deep learning segmentation and malocclusion classification methods (4–6) and application of geometric morphometric analysis to 3D skeletal imaging in disease cohorts such as cleft lip/palate (7) has opened the possibility of understanding developmental biological processes in patients and overcoming limitations of animal models that often do not reflect the human disease. The addition of 3D oral scans can improve the quantification of oral anomalies typically associated with many systemic diseases (8, 9). Very often, oral manifestations may be the earliest signs of disease or genetic anomaly and the easiest to quantify, biopsy or collect as biospecimens for detailed analysis.

Regenerative Medicine: New scaffold designs, improved imaging and technologies to track genes, cells and proteins during development and regeneration, and use of organoids as 3D miniaturized models derived from stem cells are among major innovations that are advancing regenerative medicine in the quest to replace tissues/organs lost to trauma or disease. Some ongoing activities in this space include the National Academy of Medicine Regenerative Medicine Forum started in 2016² and Armed Forces Institute of Regenerative Medicine (AFIRM), a multi-institutional, interdisciplinary network³, with opportunities for funding projects focused on wounded servicemen and women, e.g., repair of muscles, nerves and body parts (10–13).

Electronic Health Records: As the value of Precision Medicine/Individualized Healthcare has become more apparent the need for interoperable electronic health records has emerged as a key element needed for establishing accurate databases linking genomics data with other data about an individual, e.g., health history, race/ethnicity, demographics. This has resulted in significant improvements in EHR, however there have been limited attempts in the dental arena to have electronic dental records interoperable and even less related to developing platforms so that medical-dental records are interoperable. Importantly, initiatives to date indicate that interoperable electronic records result in increased preventive care visits and decreased costs associated with medical-dental diseases.

Genetics/Genomics/Proteomics: The development of sophisticated tools and technologies has resulted in an exponential growth in studies focused on identifying genes, proteins, cells, factors (host-immune responses) and microbes and in new knowledge toward understanding health and disease over a person's life span. The ability to use systematic genetic mapping in families and communities has assisted researchers in identifying genetic variants and thus, improve diagnosis and treatment, including new drugs and some gene therapy (14). Fortunately, as presented in this perspective, oral-dental researchers, in collaborations across disciplines, have taken advantage of these tools and technologies to include: improved/earlier diagnosis of certain genetic disorders, better understanding of microbial-host interactions, locally and systemically and development of salivary diagnostics for COVID-19.

¹<https://www.face2gene.com/clinic-deep-phenotypingof-genetic-disorder-dysmorphic-features/>

²<http://www.nationalacademies.org/hmd/Activities/Research/RegenerativeMedicine.aspx>

³<https://www.afirm.mil/>

on the oral cavity. Recent examples of clinical trials conducted without input from dental scientists illustrate the delays in diagnosis and potential harms in patient outcomes.

Dental Phenotypes

Individuals with genetic mutations often exhibit specific dental phenotypes (observable traits), which may be seen on oral examination. For example, individuals with hypophosphatasia (HPP), caused by mutations in the alkaline phosphatase gene, often have defects in the formation of tooth root cementum, dentin and enamel. Yet clinical trials using alkaline phosphatase enzyme replacement therapy for HPP failed to include an examination of participants' teeth (39). The effects of such therapies on the teeth are just now being analyzed. Several other disorders where oral tissues are now included in the research study have resulted in recognition of substantial oral tissue phenotypes that can lead to more rapid and earlier diagnosis and treatment (8, 40–42).

New Immuno-Cancer Treatments

Other examples of dental contributions to clinical studies and trials are related to broader effects of new therapies on oral tissues. For example, many drugs may affect salivary gland function, alter tooth color, affect mucosal function or cause oral lesions—at times so severe that patients must discontinue therapy. As a result, new drug treatments for a variety of serious

disorders require the involvement of oral health scientists as key members of the research team at the outset. The development of immune checkpoint inhibitors (ICI) to treat cancers has identified the concerning side effect of profound xerostomia after a few weeks or months of treatment (43). While this has encouraged research on how ICI disrupts salivary gland function, it underscores why inclusion of dentist scientists is critical.

Osteonecrosis of the Jaw

Without dental-medical integration the oral side effects of new therapies can take years to fathom. This was the case for medication-related osteonecrosis of the jaw (44). It has now been established that anti-resorptive drugs used not only to treat osteoporosis but also some cancers, can result in severe jaw problems as well as other anomalies of bone metabolism. The research confirming cause and effect was the result of intense cross collaboration between dental and non-dental researchers including animal studies, case reports and patient records. It is currently part of clinical endocrinology guidelines to consult a dentist when initiating these therapies, especially cancer therapies (45). Similar best clinical practices include obtaining early dental consultation prior to the initiation of head and neck radiation therapy (for oral cancers). This integration of dental with medical care has lowered the risk of the devastating side effect of osteoradionecrosis of the

jaw and improved the quality of life for patients undergoing radiation therapy.

Hospital Acquired Pneumonia

Hospital acquired pneumonia (HAP) accounts for 25 percent of all hospital-acquired infections (46) and presents a serious risk for patients hospitalized with COVID-19 (47). Studies conducted in a veterans' hospital setting have supplied evidence that non-ventilator-associated HAP was reduced significantly by providing standard oral health care (48), improving patient outcomes while lowering costs of care. This study has been expanded to include eight VA hospitals with plans for national VA deployment. While substantial evidence exists that oral health care is a modifiable risk factor for HAP and other infectious diseases, it has not been adopted universally (49, 50).

Human Papillomavirus Virus (HPV) Vaccine

This is an example where dental patient evaluation was omitted in clinical trials to evaluate the effectiveness of HPV vaccines. HPV vaccines are now recognized for their potential to prevent HPV-related oropharyngeal cancers, which have risen dramatically in recent years, especially in younger-aged groups (51). It took collaborative research efforts to reveal that this sexually transmitted disease can cause devastating manifestation in the oral cavity, and to increase research support to better understand the biologic implications of HPV +/- oral cancers. Since research has shown that some individuals are more likely to seek dental care (including for cosmetic reasons) compared with medical care, dental professionals need appropriate training so they can counsel their patients appropriately and even administer HPV and other vaccines, including COVID-19 (52). In fact, several states have approved providing vaccines in the dental setting, a view supported by the American Dental Association (53, 54).

GAINS WHEN DENTAL SCIENTISTS ARE PART OF THE TEAM

Several areas of research are benefiting from new broad-based initiatives, cross-collaborations and multidisciplinary teamwork, specifically: microbiology, salivary studies, and craniofacial anomalies.

The Human Microbiome

From the initial discoveries that dental caries and periodontal disease were associated with specific bacterial species, oral health scientists have analyzed the complex microbial communities lining oral and dental surfaces in what were called biofilms. These complex microbial communities continue to be explored for relationships with many other diseases, including malignancies (55–57). With availability of newer tools and technologies researchers have expanded their horizons beyond mapping the human genome with its 20,000 genes to explore the much larger domain of the human microbiome, including previously uncultivable microbes. The Human Microbiome Project (HMP) was launched by NIH in 2007 (58) to map the human microbiome,

choosing five sites: mouth, nasal, skin, gastrointestinal and urogenital tract. It is a stunning example of the information that can be gleaned when the dental domain is included in transdisciplinary research projects (59). One of the HMP outcomes has been a deeper awareness that microbes have a major influence on the host in health and disease, a story which is just beginning to unfold (60–68). As far as the mouth is concerned, it is a domain where oral scientists have been pioneers (69).

The *immune-microbiome complex* has become an area of intense investigation comparing the effects of a healthy vs. a diseased microbiome on the host-immune response. Intriguingly, *Klebsiella* can induce an inflammatory response in the gut, but not in the oral mucosa (60), while *Fusobacterium nucleatum*, an oral bacterium associated with severe periodontal disease, is linked to colon cancer (70). *Porphyromonas gingivalis*, a keystone pathogen in chronic periodontal disease, has been identified in amyloid plaques of individuals with Alzheimer's disease (71, 72).

The Periodontitis-Diabetes Story

The observation that patients with uncontrolled diabetes often have severe periodontitis inspired yet another major success story of the payoff when dental and non-dental researchers work together. Initial observations among the Pima tribe (73, 74) led to a focus on host-immune-microbial interactions and the key observation that in cases of uncontrolled diabetes, oral tissues, along with other tissues in the body, exhibit a hyperinflammatory response to local insults, such as infection or trauma. Addressing the hyperinflammatory issues early proved to be effective in managing, and in some cases preventing, the periodontal disease consequences of diabetes. Provision of non-surgical treatment has been associated with reductions in metabolic markers of dysglycemia, primarily glycated hemoglobin (75–77). Further, analyses of insurance databases have suggested that the provision of non-surgical periodontal treatment to persons with diabetes is associated with improved health outcomes, including reduced utilization and costs (78–80). So persuasive have been the findings from these studies that a number of U.S. insurance companies now offer additional dental care for their diabetic clients as a way to forestall more serious complications and hospitalizations. The establishment of the diabetes-periodontitis connection has important implications for addressing health disparities. Diabetes and obesity (a risk factor for diabetes) disproportionately occur in poor and minority groups. If they lack access to dental care, the impact of the two diseases will be more severe.

Salivary Diagnostics

The attractiveness of using saliva, known to contain, among other things, viral pathogens, shed cellular material (including genetic), and circulating antibodies, coupled with ease of sampling, has resulted in research targeted at detecting specific diseases or disorders and some success in the commercial development of diagnostic kits for this purpose. However, as saliva is a diluted exudate compared with blood, the amount of a given biomarker in saliva may be inadequate to detect with current tools and

TABLE 2 | Approaches toward achieving integration of oral health within the context of total health.

Collaborative and trans-disciplinary efforts are needed to integrate dental science research into broad areas of biomedical research in both the public and private sectors, where its omission has limited progress and in some cases led to adverse health outcomes (97).

Implementation science programs and learning health care systems should be deployed to ensure that the biomedical knowledge generated by an integrated research enterprise is translated into clinical practice, public policies, and consumer-directed applications, including programs to improve health literacy (19, 98). Educational efforts, along with policies that ensure equitable access to oral health care for all communities, locally, nationally and globally, can help eliminate the health disparities that persist in our nation.

The development of interoperable electronic health records (EHRs) that collectively track medical and dental health histories for patients and providers is essential to further understanding of an individual's health profile over the life span, noting risk factors, acute and chronic illnesses, and other critical information (28).

Advance Communications/Networking across disciplines: Several communities over the last few years have developed initiatives highlighting the importance of attending to all aspects of the body, including the oral region, in research, clinical care, education and policy development, in order to improve total health for all. Yet interactions and the exchange of ideas among the various constituencies are often lacking and consequently possibilities for advancing transdisciplinary approaches to health improvement are missed. Perhaps an "Oral-Systemic Health Hub" is needed where events and publications of importance to the larger community are posted regularly. For example, the Santa Fe Group has organized a *Continuum on the Benefits of Integrating Oral Health into Overall Health* [a series of webinars, a Salon and other resources on this topic (www.santafegroup.org/events)], and other groups are working on initiatives with a similar focus. And at the time of submission of this *Perspective* a Resource Library for the Integration of Primary Care and Oral Health was announced: <https://resourcelibrary.hsdm.harvard.edu/>. This site has already been populated with many publications and events. These and similar efforts reflect the mounting interest in integration and transdisciplinary approaches to health improvement which it is hoped *Frontiers in Dental Medicine* and *Frontiers in Oral Health* will continue to seed.

technologies Advanced technologies may improve that situation and indeed the advent of the coronavirus pandemic has already led to the development of safe and effective salivary test kits to detect SARS-CoV-2 in an individual (81). Symptomatic and asymptomatic spread of this virus is likely from saliva droplets and respiratory fluids (82, 83). Additionally, saliva may serve as a better source for detection of oral conditions such as oral pharyngeal HPV cancer than currently used blood tests and may be an ideal source for a "liquid biopsy" for point of care application (84–87).

Craniofacial Conditions

One of the best examples of comprehensive, collaborative care that includes dental specialists in a multidisciplinary setting is the craniofacial anomalies team. The American Cleft Palate-Craniofacial Association (ACPA) recognizes craniofacial teams who meet standards based on parameters of care that have been shown through research to provide optimal care for children with cleft lip and palate or other craniofacial anomalies. Dental specialists are integral to these teams with a direct impact on improved quality and outcomes of treatment. Several areas of research have advanced the care of children with congenital craniofacial anomalies and the understanding of disease processes leading to potential novel therapeutics for ectodermal dysplasia (88–90), promising intrauterine therapies to rescue cleft palate in mouse models (91–95), and better understanding of post-natal craniofacial development in patients with cleft lip and palate (7).

THE PANDEMIC AND DENTAL RESEARCH

While the dental community has long implemented safe practices of infection control and personalized protective equipment (PPE) resulting in very low infection rates among dentists during the pandemic (96), the potential for engaging the dental community in enhanced testing and sampling technologies is huge. Through the simple act of touching a

dental mirror to the inside cheek of a patient, a dentist can be the "point of contact" for sampling saliva as a diagnostic fluid. Additionally, biosensors incorporated in a dental mirror or toothbrush can record vital signs, including temperature fluctuations and oxygen saturation, which could detect the early presence of disease in a community. Realtime data collection from such smart tools can protect the US population by predicting early hotspots of disease, as noted by Kinsa smart thermometers during the early phase of the SARS-CoV-2 pandemic¹.

CONCLUSIONS: A CALL TO ACTION FOR RESEARCHERS, EDUCATORS AND CLINICIANS

The goal of this perspective is to increase awareness of these issues and to activate researchers, healthcare providers, economists, policy drivers, advocacy groups and the communities we serve, locally and globally, to advance collaborations across all disciplines/communities. We cannot afford to ignore data from the dental, oral and craniofacial part of the body. A few suggested action items are presented in **Table 2**.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

¹<https://www.nytimes.com/2020/03/18/health/coronavirus-fever-thermometers.html>

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Conflict of Interest: JW declares that she is a paid contractor, as a scientific writer and editor, for the Santa Fe Group.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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