ORIGINAL ARTICLE

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Personalized and precision orthodontic therapy

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Structured Abstract

Objective – To bring together orthodontic stakeholders from academics, industry, and private practice for a series of thematically focused workshops to explore and develop the transfer of novel approaches into clinical orthodontic practice.

Setting and sample population – Twenty-seven invited speakers, eight poster presenters, and participants of the Consortium for Orthodontic Advances in Science and Technology (COAST) 2014 Innovators' Workshop at the Eaglewood Resort and Spa, Itasca, Illinois, September 11–14, 2014.

Material and methods – Five themed sessions involving between 4–7 presentations followed by panel discussions were organized. The aims of the discussion sessions were to highlight important findings and consider the strength of evidence for these, indicate next steps and needed research or technological developments to move forward, and to weigh the expected benefits from these findings and steps to implement in clinical practice.

Results – Among important areas for attention identified were need for multiscale and multispecies modeling and experimentation for interspecies translation of results; large-scale collaborative efforts within the profession to address the need for adequate sample sizes for future genetic studies of complex traits such as malocclusion; a consortium approach to improve new technologies such as intra-oral scanning and 3D imaging by establishing standards; and harnessing the growing body of knowledge about bone biology for application in orthodontics.

Conclusions – With increased awareness of the potential of current and emerging technologies, translation of personalized and precision approaches in the field of orthodontics holds ever-increasing promise.

Introduction

The Consortium for Orthodontic Advances in Science and Technology (COAST) is a collaborative interinstitutional working group whose long-term objective is to foster high-caliber, cutting-edge interactions between clinicians, educators, and researchers that will lead to novel developments pertinent to orthodontics. COAST previously held five symposia between 2002 and 2012 on a range of topics, some which have been summarized in previous supplements of Orthodontics and Craniofacial Research (1–4). These previous symposia provided the foundation for focusing the next several gatherings on Personalized and Precision Orthodontics. Thus, the 2014 initiative, the 6th Biennial COAST Conference, is the first in a series of highly interactive workshops on the topic of *'Personalized and Precision Orthodontic Therapy'* and was held in Itasca, Illinois, September 11–14, 2014. A follow-up workshop to build on the 2014 outcomes will be held in 2016. These workshops address the current challenges of how to harness the burgeoning and exciting information and technological developments to provide the best available individualized orthodontic care to our patients.

Thematically focused workshops on the applications of new computer-based technologies and biomedical advances to patient care and convening diverse experts to explore and develop the transfer of novel approaches into clinical practice are current models being used successfully for progress in other fields. For example, the National Research Council recently published a landmark report entitled 'Toward Precision Medicine' (5). This report was the outcome of a 2-day workshop held March 1–2, 2011 to develop a framework for a new taxonomy of disease that reflects modern capabilities in terms of 'data-intensive biology and rapidly expanding knowledge of the mechanisms of fundamental biological processes'. With its previous successes serving as a springboard, COAST utilized a similar approach with the aim of helping the orthodontic profession keep pace with and apply advances in genetics, molecular biology, engineering and technology to enhance the delivery of personalized and precision orthodontic care. Thus, the theme of the series of workshops strongly fits the current needs of the orthodontic profession and reflects the cutting-edge approaches being applied to advance biomedical research and patient care in other healthcare fields.

Main topics presented and discussed at the 2014 COAST Workshop

The 2014 Workshop brought together orthodontic residents, postdoctoral fellows, clinicians in private practice, educators and researchers, plus individuals with commercial interests in orthodontic techniques and technologies. These individuals were highly interactive during the 5 half-day themed sessions as well as during social events from September 11 to September 14, 2014. For each half-day themed session, between 4 and 7 invited speakers presented their data and analyses followed by questions and comments from the audience. The end of each half-day sessions was summarized by a panel discussion, where members of the audience put forward questions to the assembled panel of speakers and both audience members and speakers engaged in discourse.

'The Challenge and the Promise of Precision Orthodontics' was the title of the keynote address given by Sunil Kapila (University of Michigan). This address included a history of COAST and outcomes of the five previous conferences (2002–2012), which set benchmarks for technology transfer to clinical orthodontics, for example, by heralding the use of three-dimensional imaging, facilitating the integration of clinical

needs and industrial design that resulted in one of the first commercially available cone-beam computed tomography systems, tissue engineering science leading to clinical trials for replacement craniofacial structures, and potential pharmacological approaches for enhancing bone biology and orthodontic tooth movement. Dr. Kapila introduced several important areas for personalized and precision orthodontics, specifically through advancements in genetics, technology, and bioactive molecules and offered projections on how these could be applied in the future.

The 1st themed session was *'Mechanotherapy and Therapeutic Techniques: Living in a Complicated and Demanding 3D World'* and featured five speakers. Mani Alikhani (New York University) led in this series with his presentation on the 'Impact and indications for accelerated tooth movement'. In his talk, Dr. Alikhani covered prospects and evidence for accelerating tooth movement and promoting bone formation via controlled local introduction of repeated micro-perforations in both murine and human models. The basis of this approach is to achieve more continuous stimulation of active agents, such as cytokines, to stimulate osteoclast as well as osteoblast formation and activity in the area of desired tooth movement and/or bone change. Dr. Alikhani finished with some evidence that locally introduced micro-vibration may offer bone anabolic effects. This was an appropriate segue to the presentation by Dubravko Pavlin (University of Texas Health Sciences at San Antonio), which was titled 'Prescribed vibration: If it works, what do the data look like'? Dr. Pavlin provided some apparently positive pilot clinical data for bone catabolic effects resulting in faster average tooth movement associated with applied vibratory forces (25 cN, 30 Hz) delivered via a handheld device for 20 min/day after 30 days. Next, Thorsten Grunheid (University of Minnesota) covered the topic of 'Personalized orthodontic appliances: Where are we headed and why we need them'. Dr. Grunheid examined the evidence for treatment outcomes showing the possibility for decreased treatment time without increased undesirable side effects based

on comparisons between personalized vs. conventional orthodontic appliances. Although currently it may be relatively difficult to achieve some types of tooth movement via the available individually customized appliances, Dr. Grunheid pointed out that any systems which improve clinicians' abilities to visualize and simulate treatment goals ahead of time could lead to improved design of appliances, treatment plans and ultimately have potential to improve communications and patient care. Lucia Cevidanes (University of Michigan) showed how she and her collaborators are using three-dimensional surface models of temporomandibular joint (TMJ) structures to characterize anatomical differences via color maps. In her presentation 'TMJ condylar osteoarthritis correlates with specific systematic and local biomarkers of disease', Dr. Cevidanes showed how image analysis in this field is moving forward to include measurable biomarkers linked to bone loss and formation with the goal of early detection of degenerative joint processes. The first session was concluded with a presentation from Jie Chen (Indiana University-Purdue University Indianapolis) entitled 'Finite element analysis for clinical orthodontics'. Dr. Chen demonstrated how collaborations between engineers and clinicians resulting in useful finite element modeling tools can effectively elucidate comparisons between stress distributions within root, periodontal ligament, and bone tissues when teeth are orthodontically loaded. The discussion that followed these presentations focused on the importance of integrating new evidence to concepts of orthodontic tooth movement and bone changes and continuing to challenge conventional 'wisdom' in the light of new evidence. There was attention paid to between-species differences in these phenomena of tooth movement and bone change, and to the need for multi-animal models for cross-species comparisons. With the advent of new technologies for three-dimensional imaging, issues of reliability and quantitative limits associated with voxel size were noted, as was a call for combining information from multiple modalities to improve characterization of clinical conditions. Finally, due to

the escalated awareness of the complexity and redundancy of the bone turnover and change processes, there was considerable discussion about which biological pathways to focus on for effective clinical improvements. Matters of genetics, molecular biology, and new technologies for assaying multiple factors were raised.

The 2nd themed session was '*Instrumentation, Scaffolds and Robotics: From Cold Steel to Stem Cells*', featuring four speakers. Zonyang Sun (The Ohio State University) provided novel data on 'Improving distraction osteogenesis' via mesenchymal stem cell transplantation to enhance craniofacial deficiencies. Dr. Sun demonstrated early results in a porcine model aimed at shortening treatment time in future clinical applications. Dr. Sun proposed that customized cell transplantation according to genotype plus optimized cell sources, types, and quantity could improve surgical results in future. This was followed by Michael Detamore's (University of Kansas) presentation on 'TMJ scaffolds: Where are we headed'? Dr. Detamore provided a survey of the history of TMJ tissues engineering, pointed out unique features such as the anisotropy of the cartilages of the disk and condyle, and explained how new enhancement methods are being used, such as increased carbon dioxide pressures for microsphere grouping and three-dimensional printing of scaffolds. Stephen Yen (University of Southern California) explored the 'Clinical effectiveness of late maxillary protraction', specifically focusing on Class III malocclusions in patients with cleft defects. The main question posed was: Can protraction of the maxilla be accomplished in these patients via mobilization of the sutures and stimulation of fibrous tissues, ultimately improving skeletal relations earlier than surgery permits and possibly avoiding orthognathic surgical procedures altogether? Dr. Yen showed encouraging results from pilot studies to compare the results of this approach with those of surgery and no treatment. This lead to Tung Nguyen's (University of North Carolina at Chapel Hill) presentation '3D evaluation of orthopedic changes resulting from bone anchored maxillary protraction'. Dr. Nguyen covered the evidence for age sensitivity,

response differences among sutures, quantification of dentoalveolar compensation vs. bony displacement, and importance of compliance. The discussion that ensued first addressed prospects for reverse modeling, starting out with desired end results, calculating the stresses needed to achieve these and then designing appropriate appliances, for example, pre-programmed rapid palatal appliances. This led to considerations of biologically active agents incorporated into graft materials and/or delivered locally at sites of desired change, such as bone morphogenetic proteins for promoting bone formation and mesenchymal stem cells for faster bone mineralization. Finally, matters of how to assess longitudinal changes in 3D vs. 2D and the associated challenges were covered.

The 3rd themed session was '*Genes and Personalized Orthodontics: Spit Out Your DNA Please*' and featured seven speakers. Sylvia Frazier-Bowers (University of North Carolina at Chapel Hill) spoke about 'Finding the pathway of least resistance: Optimal diagnosis, treatment, and approaches for eruption disorders'. Dr. Frazier-Bowers elucidated the importance for orthodontists to distinguish between mechanical eruption failure, ankyloses and primary failure of eruption prior to starting treatment. She provided evidence for how 'personalized medicine'—that is, an individualized profile of a person's genes and history—can be applied effectively to diagnose primary failure of eruption. James Hartsfield (University of Kentucky) further illustrated the potential effectiveness of this 'personalized' approach in his presentation 'Genetic and treatment related risk factors associated with external apical root resorption (EARR) concurrent with orthodontia'. More specifically, genetics as a clinical tool was illustrated by Dr. Hartsfield using the findings to date, where four single nucleotide polymorphisms together explain about 25% of the EARR variability in a population of post-orthodontic treatment patients, whereas length of treatment accounts for about 10% of the EARR variability in this population. Next, the participants heard Scott Conley (University of Michigan) present on 'Management of sleep apnea: A critical look at

efficacy and long-term effects of intra-oral appliances'. Dr. Conley explained the role of the orthodontist in an interdisciplinary team approach to proper diagnosis and management of adult sleep apnea cases. Lina Moreno-Uribe (University of Iowa) shared the work of her research team in the area of 'Candidate gene analyses of 2D dento-facial phenotypes in patients with malocclusion'. Dr. Moreno-Uribe showed how well-characterized dentofacial features combined with knowledge from animal models of craniofacial variation and gene analyses may lead to more specific diagnostic information about malocclusions that could be used to prevent development or improve treatment of these malocclusions in the future. James Sciote (Temple University) continued this focus in his presentation 'Associations between ACTN3 and OPPERA pain process genes in malocclusion'. Dr. Sciote described his collaborative work investigating the possible roles of important musculoskeletal and pain genes in the development of specific phenotypes commonly treated with orthodontics. This session was concluded by Andrew Lidral (University of Iowa) who presented 'Advances in understanding the genetics of clefting', with the focus on lip clefting with/without palate clefting. Dr. Lidral shared what he has learned using multispecies approaches to uncover candidate genes and genetic elements linked to phenotypes of interest and why personal genome- or exome-wide studies have been indicated to continue on this road to discovery. The panel discussion that ensued covered matters of affordability of genetic testing; how the large samples sizes required for multiple gene analyses and gene–gene interaction studies to further elucidate the genetic basis for malocclusions may require orchestrated efforts by the orthodontic profession; current vs. future treatment for primary failure of eruption, EARR, and malocclusions; how to elucidate the basis of complex traits through studying genotypes in families in concert with function studies using animal models; indications for documenting orthodontic stimuli quantitatively along with dentofacial phenotype for future success of precision orthodontics; and concluded by agree-

ment of the group that orthodontists need to be well educated for the best chance of successfully integrating 'personalized orthodontics' into clinical practice.

'Imaging: Using the Data That's On the Surface or Hidden Below' was the 4th themed session and featured four speakers. Sarandeep Huja (University of Kentucky) covered 'Bone anchors' and the history of endosseous vs. mini-screw implants, what quantitative variables should be considered and what amounts of these variables are necessary for success. Dr. Huja pointed out the need to recognize differences in animal models to compare properly results of studies involving different species. He also discussed clinical clues to evaluate bone quality and mini-screw stability for orthodontic anchorage. '3D surface imaging technology for orthodontic records' was presented by Sercan Akyalcin (University of Texas Health Sciences Center at Houston). Dr. Akyalcin covered the advantages and limitations, plus the applicability of this technology to research and clinical practice. David Covell, Jr. (Oregon Health and Science University) followed with the presentation 'Accuracy of alveolar bone measurements from cone beam computed tomography obtained at multiple settings', Dr. Covell covered the effects of voxel sizes and scan times on the accuracy of measurements and the estimated radiation dosages. To wrap-up this session, Yoly Gonzalez (University at Buffalo) summarized 'New diagnostic criteria for temporomandibular disorders'. Dr. Gonzalez provided supporting evidence from validation studies, which shows that imaging combined with clinical examination data are now the gold-standards for characterizing temporomandibular disorders (TMD). These presentations were followed by lively discussion. Part of this discussion pointed to the burgeoning options for intra-oral scanning via either video or photographic capture, the importance of stitching algorithms and the pros/cons of the various file formats available, plus the need for collaboration to establish standards in this arena.

The 5th and final themed session was 'Multiscale and Environmental Human Modeling: Tools

for Understanding Human Conditions and Testing Clinical Therapies' and had six speakers. Jeffrey Nickel (University of Missouri-Kansas City) presented 'Computer modelling of CNS muscle organization'. Dr. Nickel explained the rationales behind the numerical methods and biological objective functions used, how the models predict individual-specific muscle and joint forces for static jaw loading conditions, validation of these results using *in vivo* data, and the applicability of these numerical models to improve understanding of clinical problems. Hai Yao (Clemson University) expanded on this with the presentation. 'Computational techniques: When you can't do an experiment … model the problem'! Dr. Yao showed how patient-specific anatomy, kinematics and loading can be combined to study joint mechanics, nutrition, gaseous exchange and chemical signaling on multiscale levels. Furthermore, he showed how these approaches can be used to compare properties between species. Luigi Gallo (University of Zurich) presented clinical data about joint tissue contact mechanics from modeling approaches using dynamic stereometry, a combination of individual-specific imaging and kinematics. Dr. Gallo's presentation was entitled as: 'TMD diagnostic group differences in TMJ disk energy densities during symmetrical mandibular closing movement'. To complement this, Laura Iwasaki (University of Missouri-Kansas City) presented 'Masticatory muscle duty factors in humans'. Dr. Iwasaki demonstrated measures of behavior, namely muscle use, by those with and without TMD in their natural environments. Next, Rodrigo Viecilli (Loma Linda University) presented 'Application of finite element technique: Individualized characterization of periodontal mechanics during tooth movement'. Dr. Viecilli illustrated how this modeling approach can be used to calculate and customize force delivery appropriate for specific teeth to achieve defined treatment goals. The final presentation was by Nan Hatch (University of Michigan) who spoke about 'Molecular biology in private practice: What can we expect in 2024'? Dr. Hatch presented the results of her studies with collaborators, demonstrating the application of biological

agents involved in the RANK–RANKL–OPG pathway, to control bone resorption and formation. She further reviewed candidate mediators of bone anabolism/catabolism from the growing body of work in the bone research arena that could be potentially important to future orthodontic treatment and retention. This last half-day session closed with a panel discussion and question period, in which, for example, injectable biologically active agents were considered along with management of associated discomfort. Features of mutual interest were highlighted, pointing to future studies and potential new collaborations.

Conclusions and charge for the 2016 COAST Workshop

Closing remarks by the COAST Scientific Advisory Board followed the final session to wrap-up the 2014 Workshop and set the stage for the follow-up Workshop in 2016. Among important areas for attention identified were as follows: need for multiscale and multispecies modeling and experimentation for interspecies translation of results; large-scale collaborative efforts within the profession for future genetic studies of complex traits; a consortium approach to improve new technologies by establishing standards; and harnessing the growing body of knowledge about bone biology for application in orthodontics. With increased awareness of the current and emerging technologies, facilitated translation of approaches toward personalized and precision orthodontics holds ever-increasing promise. The filing of patents for clinically viable products and the engagement of partners in industry will help expedite the transfer of these discoveries to the betterment and specificity of patient care.

Clinical relevance

The Consortium for Orthodontic Advances in Science and Technology (COAST) 2014 Innovators' Workshop on Personalized and Precision

Orthodontic Therapy aimed to address the current challenges of how to harness the burgeoning and exciting information and technological developments to provide the best available individualized orthodontic care to patients. Expected direct results of this and the follow-up 2016 Workshop include 1) a position paper establishing standards for the profession on use of personalized and precision orthodontics in clinical practice, 2) a technology transfer plan to develop and improve useful clinical products for personalized and precision orthodontics, and 3) peer-reviewed and published proceedings to provide widespread dissemination of the information derived from the workshops and to promote focused research activity in this thematic area. This issue of *Orthodontics and Craniofacial Research* addresses the latter outcome for the 2014 Workshop.

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