Translational Systems Approach to Clinical Dental Research: A Primer for Precision and Personalized Oral Health in Resource-Constrained Settings

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Key words: Clinical Dental Research, Translational Dental Research, Artificial Intelligence, Africa, Precision Oral Health, Systems Approach

ABSTRACT

Resource-constrained areas, such as sub-Saharan Africa, urgently need to make use of cutting-edge methods for providing dental treatment and research while making the most of their limited resources. The principles of clinical dental research (CDR) and the enhancement of a translational dental research (TDR) pipeline are not widely used or taken into consideration, even though a great deal of clinical dental research has emerged in Africa using clinical dental samples (or data) and conducted by dental healthcare personnel. However, many dental schools across the continent do not have curriculum-integrated methods that follow this idea. The continent's future dentists urgently need to be prepared with strong clinical dentistry research abilities in an integrated, systematic approach.

The correct definition of CDR, including its scope and objectives, is crucial, as is the reason for conducting this kind of study. In the age of precision and omics-based dentistry, it is also necessary to define essential ideas in TDR, precision, and personalized oral health (PPOH). As a result, this study presents and discusses models and an integrative implementation framework for maximizing the use of TDR for economical CDR in settings with restricted resources. We also suggested using a CDR and TDR model that integrates CDR, TDR, and PPOH in a multiscale, systems-oriented manner in dental research settings and clinical dentistry practice settings. Additionally, we suggested incorporating these ideas into the undergraduate and graduate dental programmes' pedagogical curricula.

Cost- and labor-effective practices are intended to be implemented using the suggested integrated implementation framework for CDR and TDR in resource-constrained regions. Even yet, PPOH and one health should be successfully included into CDR and TDR in order to improve oral health globally and reform oral health systems in Africa.

INTRODUCTION

The fundamental phenomenon of scarcity has plagued human civilizations since time immemorial and is particularly relevant in an anthropocentric post-COVID era.[1-4] Two key concurrent contributors to scarcity are limited resources and unlimited needs and wants.[5, 6] A setting in which the infinite human needs are tempered by the finite reality of the canonical factors of production (such as land, labour, entrepreneurship, and capital) always demands innovation, investments, and plan for growth.[5, 7] Hence, resource-constrained regions such as sub-Saharan Africa urgently need to leverage innovative approaches to dental care provision and research, using scarce resources.

Although so much clinical research has emerged in Africa using clinical dental samples/data; and carried out by dental healthcare personnel with varying levels of experience, the principles of clinical dental research are seldom taught in a modular or curriculum-integrated manner in many academic dental schools on the continent. To date, there is a dearth of papers (or works) addressing the knowledge gap in the best practices of clinical dental research (CDR) for precision oral health, particularly in low-and middle-income countries. A two-part series on the research methodology in dentistry was published with a focus on the essential principles of and relevant statistical approaches to dental research, respectively[8,9]. Though mainly focused on dental research in India[8] and not explicitly directed to CDR, the motivation for the series was to improve knowledge in the field of dental research. It attempted to bridge the publication gaps arising from the paucity of Indian dental research articles published in scientific international peer reviewed journals. The authors mentioned that there is no specialty for dental research in India and that research is only a systematic way of reasoning, analyzing, and presenting clinical findings from routine clinical practice.[8]

Currently, the degree of integration of CDR into mainstream biomedical research is low, leading to siloed research processes, clinical practice and education, to the detriment of the healthcare providers, patients, and policy makers.[10] Although CDR is not a well-defined discipline in sub-Saharan Africa, equipping future dental professionals on the continent with robust clinical dental research skills need to be implemented in a systematized manner. In addition, emerging precision oral health and systems biology tools are essential to optimize dental healthcare delivery in resource-constrained settings.

It is important to know what exactly clinical research should entail, and what the purpose of carrying out research is in line with Albert Einstein's quote; “If we knew what we were doing, it wouldn't be called research, would it?”, hence, dental research needs to be carried out in a data-agnostic manner. [11, 12] This paper therefore aims to describe the basic CDR workflow in dentistry and in the process, describe key concepts in translational research, systems biology, and personalized medicine in the context of precision oral health.

CLINICAL AND TRANSLATIONAL DENTAL RESEARCH

Although clinicians in the field of dentistry typically carry out research in various recognized disciplines, the field of clinical dental research lacks clear definition, as compared to clinical research in medicine. Hence, foundational principles for CDR urgently need to be established in resource-constrained settings. Be that as it may, these principles need to be prescribed and incorporated into the undergraduate and postgraduate dental education curriculum of institutions in these regions.

DEFINITION OF CLINICAL RESEARCH

The National Cancer Institute (NCI) dictionary defines clinical research as "Research in which people, or data or samples of tissue from people, are studied to understand health and disease. Clinical research helps to find new and better ways to detect, diagnose, treat, and prevent disease."[13] and Clinical trials, which test new treatments for a disease, natural history studies, which collect health information to understand how a disease develops and progresses over time.[13] Most CDR in sub-Saharan Africa generally follows (by extension) many of the principles defined by the NCI already, however there is a need to define CDR and its parameters. One problem to consider ab-initio is the index of suspicion and distrust that people of African origin have for participating in research. [14-16] For instance, a study involving 176 adults at University of Missouri, Kansas City (UMKC), showed that African-Americans and participants with lower levels of education were likelier to be reluctant to participate in dental clinical trials.[17] This situation requires dental practitioners to focus on educating colleagues and the general populace about the benefits of CDR to society.

CLINICAL RESEARCH FIELD COVERAGE

Within the context of NCI's definition, clinical research has a wide coverage and application for a range of health fields that are important to clinical practice. In addition to clinical domains, other apparent public health fields such as epidemiology,[18] biostatistics,[19] decision science [20] and health policies [21, 22] are also included. The basic medical science fields of anatomy[23], biology[24], pathology,[25]and chemistry [26,27] also form key components of clinical research, inter alia. Less apparent fields such as artificial intelligence,[28-30] human factors,[31] and behavioral sciences, [32, 33] have also found their place in the clinical research domain. This list is not exhaustive but highlights additional areas of CDR that can be explored beyond the ambit of epidemiological research approaches currently available and practiced in resource-limited regions. CDR needs to expand into other realms of research to be able to fulfil its mandate as a well-defined discipline and this must translate into teaching curriculum and clinical dental practice. This approach will ensure that newly trained dental professionals are well equipped with the principles of CDR which can be readily translated into practice.

DEFINITION OF TRANSLATIONAL RESEARCH

Translational research (TR) is often used interchangeably with translational medicine, clinical translation science, and bench-to-bedside research among many researchers.[34, 35] TR involves the process by which observations at the basic laboratory, clinical practice and community levels are converted to innovative interventions that can improve individual and public health. These interventions may include therapeutic and diagnostic tools as well as behavioral change practices and new medical/surgical procedures.[36] More formally, TR has been described by the National Center for Advancing Translational Sciences (NCATS) as research that promotes the advancement of knowledge gleaned from laboratory bench to bedside and then to the community along the basic sciences research to population health research continuum.[37,38] Safety, efficacy and efficiency of the intervention must be ascertained at every level of the TR.[39] TR is a representation of stages of research that spans from the basic biological research domain to clinical interventional research that are geared at improving health at all levels (individual and population health). In fact, some scholar would consider wider areas of translational medicine to include knowledge transfer (translation) dissemination, quality improvement and health services research, as part included in TR.[40-43] Patient involvement is the most critical feature of every stage of TR,[44-46]

although it permits stages to build evidence in an incremental manner and hence may take a unidirectional [43,47] or a more nuanced, integrated, non-linear approach.[46, 48] TR improves the quality of CDR and it plays crucial role in ensuring a reduction in biomedical and dental research wastage[39] (**Figure 1**).

Figure 1. A proposed nonlinear model of translational dental research (TDR) from basic laboratory research (T0), through the T1-T4 phases which translate from human to community implementation. TDR improves the quality of clinical dental research (CDR) and reduces wastage of limited resources available for CDR in resource-constrained settings.

Faggion[39] discussed the importance of TR in clinical dental procedures, and reviewed the sequence and directionality of TR phases (whether it is always from basic to clinical, or vice versa); as well as the chronological order in which these research are published.[39] It was observed in this study that TR principles were not well followed in many CDRs, and that besides poor evidence and lack of quality assurance, some studies carried out human research before animal research. It is thus paramount that oral health professionals are familiar with the normative sequence, nuances and interdependence of CDR and TR in the era of precision oral health. The next section is an adaptive juxtaposition of the stages of TR for CDR, thus proposing some guiding principles for the proper practice of TR for CDR in resource-constrained settings, where wastage of scarce resources is practically unaffordable.

THE TRANSLATIONAL DENTAL RESEARCH MODEL

Previous models for translating basic research have focused on advancement of basic laboratory research to clinical research and then to population level research.[49, 50] This model was initially effective in meeting important clinical needs and bridging biomedical research gap using investigative teams in these three domains. It however became evident that operating in these 3 separate structural domains inadvertently resulted in functional research silos and lack of collaborative and multidisciplinary approaches to solving fundamental clinical research problems.[48] Hence, there is a pressing regional need for "trans-disciplinarity", better communication, and training of astute clinician-scientists to improve TR in sub-Saharan Africa.

Then came the dispensation of sequential TR that prescribes a bench-to-bedside-to-community continuum for practicing TR.[46] This model describes TR as occurring in four distinct phases (viz, T0-T4) that connects basic research to its ultimate translation into the benefit of patients and the general populace. T1 phase involves the potential clinical translation of basic laboratory research work (T0) to generate knowledge in regards of a potential therapy or intervention. This might include the development of a novel drug for the treatment of a condition, or a Phase 1 clinical trial that seeks to assess the safety of such a drug or intervention in a small population. [51] The T2 phase involves studies that seek to investigate the efficacy of a novel intervention or drug in a larger human population, carried out under optimized conditions (Phase 2); or a comparative Phase 3 study between a novel drug and the current standard of clinical practice.[43] Once the efficacy of the intervention is ascertained under a controlled clinical setting, then the T3 translational workflow phase requires the intervention to be moved

out to a real-world setting (e.g., primary or community health clinics) for implementation.

Finally, T4 phase involves evaluation of the population-level assessment of the public health benefit of the new intervention and potential to roll out programs and policies based on the T4 TR.[43] The success of this sequential TR model is dependent on partnership and knowledge exchange between scientists, clinicians, community, and policy makers.[48] The linearity assumption also is a major drawback of this model. A unidirectional flow creates a restrictive feed-back loop that does not leave much room for restructuring and recalibrating of innovation along the TR continuum. For example, clinical TR findings at T1 or T2 may lead a clinician-scientist to further investigations using a basic laboratory research (T0) approach. The interconnectedness of CDR and TDR demands a TR-dependent value proposition for improving CDR in resource-constrained settings. Hence, it is being proposed in this review that more attention be paid to translational dental research (TDR) as we transition into the era of precision oral health and artificial-intelligence driven data science.

Concerted efforts and intergovernmental initiatives are needed in African dental schools to improve knowledge of TDR and its nexus with good CDR, to avoid wastage and fragmented approaches at solving a multifaceted complex problem. The good news is that infrastructural capacities already partially exist on the continent that can be leveraged for building the routine practice of TDR in African dental settings. Despite the controversy, the advent of natural language processing (NLP) chatbots based on large language models such as the OpenAI's ChatGPT, GPT-3.5 and -4 is beginning to revolutionize medical education and clinical practice. [52-57] Dental sciences and oral healthcare in Africa must not miss out on the benefits of AI. [58] Also, the burgeoning omics field, virtualized computing platforms, and big dental data calls for a more nuanced way to envision TDR. Beside pedagogical implementation of a TDR-integrated curriculum both at undergraduate and postgraduate levels, early-stage oral health investigators and junior faculty need to be orientated about the nuances of TDR and its crucial importance in the practice (and principles) of precision oral health implementation in resource-constrained settings.

PRECISION AND PERSONALIZED ORAL HEALTH

Precision oral health has been described as a data-driven, multifaceted, and contemporary approach to oral healthcare using individual characterization for patient stratification, meaning that patients with similar phenotypes are grouped together. [59, 60] This approach can be described as one that takes individual variations into careful consideration. For example, in the African context, the orthodox pathology diagnostic pipeline involves patients' biopsied tissue processing and staining with Hematoxylin and Eosin, after which it would be viewed under a microscope to obtain cellular and histopathological patterns.[61-63] Despite advances in many centers, this is what obtains in many African countries. Precision oral health indicates a multifaceted data-driven approach to tease the molecular risk-profile of patients apart for providing customized treatment for patients based on risk profiles, instead of using a "one-size–fits-all" approach. Personalized medicine is an approach to medicine that employs information about an individual's genes, proteins, and environmental exposure to diagnose, treat and prevent disease. [64-67] This approach uses molecular information to manage disease in an individualized manner. This indicates that

therapeutic options must not be limited to one for all patients, but rather be stratified for individuals and then molecularly profile them before commencing treatment. This approach, which has been widely practiced in medicine and is beginning to find application in oral health- birthing the field of personalized oral health. [68-71] In a rapidly evolving TDR and CDR landscape, it is proposed that ancillary concepts such as precision and personalized oral health (PPOH) should be integrated in a systems-oriented manner to achieve the optimal benefit of TDR and CDR in resource-limited settings (**Figure 2**).

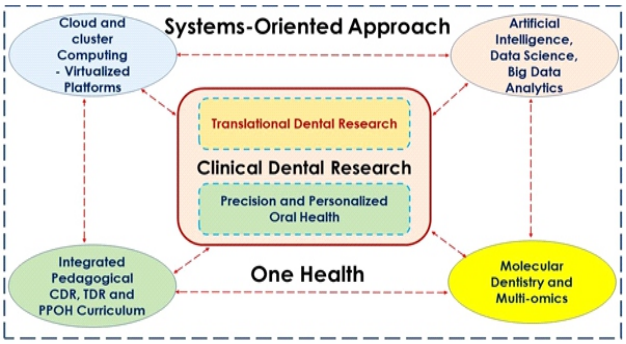

Figure 2. A proposed framework for Clinical Dental Research (CDR) that has a central component of Translational Dental Research (TDR) and Precision and Personalized Oral Health (PPOH). This framework benefits from ancillary tools such as molecular dentistry and multiomics; emerging artificial intelligence and data science tools; virtualized could computing; and a integrated pedagogical undergraduate and postgraduate curriculum that provide dental training in CDR, TDR, and PPOH. All must operate in a systems-oriented manner and should be considerate to one health principles.

The systems approach to TDR and CDR will permit a multiscale and multidimensional interrogation and understanding of oral diseases in these settings. Systems-level TDR should also dynamically permit PPOH model representation in the abstract, reality and virtual realms.[72] PPOH requires the dynamic, temporal, interdisciplinary, multiscale, integrated application of complex biological systems, using large scale quantification of the full complement of biomolecules in a system, from the atomic level to the biosphere.[73, 74] In addition, there are potential interactive overlaps between human, animal, and environmental health, resulting in the emerging field of "one health" which potentially has application in TDR and CDR.[75-77] Indeed, there are glaring interdependencies between the health of humans and animals and the environment. This key lesson is well illustrated by the novel coronavirus-19 (COVID-19) pandemic, which initially originated from an infected bat before transmission to humans .[78-81] While the traditional TR pipeline emphasizes the centrality of human involvement in its definition, [43, 82, 83] we envision a dynamic TDR that incorporates an integrated systems approach for a holistic delivery of dental care using PPOH-considerate CDR, in the era of precision oral health. It is also imperative to incorporate this integrated approach in redefining pedagogical approaches in undergraduate and postgraduate curriculum design. For example, Linder and co-workers presented an implementation model for a one health course at Tuft University that converged different faculties from several fields including dental, medical, veterinary and nutrition for undergraduate curriculum design.[77] The success of their program and the broad-based enlightenment of undergraduate students on one health concepts and implementation alludes to the immense benefit of an integrated approach in tackling multifaceted societal oral health problems. Such a one health model can be expanded for a systems-oriented and holistic approach to TDR and CDR in Africa.

CONCLUSION AND RECOMMENDATIONS

The critical shortages of infrastructure and research funding in resource-constrained regions requires a strategic practice of cost-effective TDR and CDR that harnesses the benefits of PPOH, using a systems-oriented approach. An important gap in knowledge of how these concepts complement each

other needs to be addressed among dental health practitioners in sub-Saharan Africa and other low-and-middle income countries of the world. This would involve and integrated TDR and CDR curriculum that puts the emerging AI and data science tools,[58] systems biology [72] and one health [75] concept into consideration.

For the successful implementation of a pragmatic CDR that is TDR-based in the African setting, a carefully curated list of interventions and recommendations that will potentially improve the routine clinical utility of molecular and omics dentistry in Africa and other resource-constrained settings, have been described elsewhere.[84, 85] A study can only be as good as its study design, hence, good CDR and TDR should always be started from a well-crafted research question using the FINER principle, which emphasizes criteria such as **f**easible, **i**nteresting, **n**ovel, **e**thical, and **r**elevant. [86, 87] Close attention should also be paid to careful data curation, collection and processing plan that are instituted. Skill set development is another vital ingredient, hence the training of dentist-scientists and dental research personnel is key.[85] This would help the analytical implementation and interpretation capacity of emerging oral health big data generated on the African continent.

Despite the extensive achievement in CDR in many resource-constrained regions, more work is still needed to bridge the dearth of TDR and PPOH-oriented CDR work and the chasm between oral health and general health, which often leaves oral health out as a global population health priority. [88-91] Using the proposed integrative implementation framework for CDR and TDR in resource-constrained regions of the world, it is hoped that cost and labour effective practices will be instituted and discussions on effective incorporation of PPOH into clinical dental healthcare delivery will be incorporated into oral health policies and systems reform in Africa.

REFERENCES

1. Folke C, Polasky S, Rockström J, Galaz V, Westley F, Lamont M, et al. Our future in the Anthropocene biosphere. Ambio. 2021;50(4):834-69.
2. Nazarenko S, Kriaučiūnienė J, Šarauskienė D, Jakimavičius D. Patterns of Past and Future Droughts in Permanent Lowland Rivers. Water. 2022;14(1):71.
3. Shang Y, Li H, Zhang R. Effects of Pandemic Outbreak on Economies: Evidence From Business History Context. Front Public Health. 2021;9:632043.
4. Hempel S, Burke R, Hochman M, Thompson G, Brothers A, Shin J, et al. Allocation of scarce resources in a pandemic: rapid systematic review update of strategies for policymakers. Journal of Clinical Epidemiology. 2021 Nov 1, 139:255-263.
5. Ghosh S. Time, scarcity, and abundance. Front Res Metr Anal. 2022;7:974706.
6. Fanning Z. "Socialization for Scarcity" in Emergency Management: Rethinking Assumptions of Resource Scarcity in Humanitarian Crises. Ann Glob Health. 2023;89(1):24.
7. Adam NA, Alarifi G. Innovation practices for survival of small and medium enterprises (SMEs) in the COVID-19 times: the role of external support. Journal of Innovation and Entrepreneurship. 2021;10(1):15.
8. Krithikadatta J. Research methodology in Dentistry: Part I - The essentials and relevance of research. J Conserv Dent. 2012;15(1):5-11.
9. Krithikadatta J, Valarmathi S. Research methodology in dentistry: Part II - The relevance of statistics in research. J Conserv Dent. 2012;15(3):206-213.
10. Mouradian W, Lee J, Wilentz J, Somerman M. A Perspective: Integrating Dental and Medical Research Improves Overall Health. Frontiers in Dental Medicine. 2021;2.
11. Mozersky J, McIntosh T, Walsh HA,

Parsons MV, Goodman M, DuBois JM. Barriers and facilitators to qualitative data sharing in the United States: A survey of qualitative researchers. PLoS One. 2021;16(12):e0261719.
12. Farnum MA, Ashok M, Kowalski D, Du F, Mohanty L, Konstant P, et al. A cross-source, system-agnostic solution for clinical data review. Database (Oxford). 2019;2019:baz017.
13. NCI. National Institute of Health; [Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/clinical-research.
14. Durant RW, Legedza AT, Marcantonio ER, Freeman MB, Landon BE. Different types of distrust in clinical research among whites and African Americans. J Natl Med Assoc. 2011;103(2):123-30.
15. Warren RC, Shedlin MG, Alema-Mensah E, Obasaju C, Hodge DA. Clinical Trials Participation Among African Americans and the Ethics of Trust: Leadership Perspectives. J Healthc Sci Humanit. 2020;10(1):104-123.
16. Scharff DP, Mathews KJ, Jackson P, Hoffsuemmer J, Martin E, Edwards D. More than Tuskegee: understanding mistrust about research participation. J Health Care Poor Underserved. 2010;21(3):879-897.
17. 1Friesen LR, Williams KB. Attitudes and motivations regarding willingness to participate in dental clinical trials. Contemp Clin Trials Commun. 2016;2:85-90.
18. Manja V, Lakshminrusimha S. Epidemiology and Clinical Research Design, Part 1: Study Types. Neoreviews. 2014;15(12):e558-e569.
19. Barkan H. Statistics in clinical research: Important considerations. Ann Card Anaesth. 2015;18(1):74-82.
20. Hilden J, Habbema JD. The marriage of clinical trials and clinical decision science. Stat Med. 1990;9(11):1243-1257.
21. Rahman H. Influence of Research on Health Policy and Clinical Practice. J Obstet Gynaecol India. 2017;67(5):319-323.
22. Engelman A, Case B, Meeks L, Fetters MD. Conducting health policy analysis in primary care research: turning clinical ideas into action. Fam Med Community Health. 2019;7(2):e000076.
23. Jones DG, Dias GJ, Mercer S, Zhang M, Nicholson HD. Clinical anatomy research in a research-driven anatomy department. Clin Anat. 2002;15(3):228-232.
24. Bielekova B, Vodovotz Y, An G, Hallenbeck J. How implementation of systems biology into clinical trials accelerates understanding of diseases. Front Neurol. 2014;5:102.
25. Robinson P, Bacon CM, Lim SJ, Shaaban AM, Brierley D, Lewis I, et al. Assessment of clinical trial protocols for pathology content using the SPIRIT-Path guidelines highlights areas for improvement. J Pathol Clin Res. 2022;8(5):411-421.
26. Duburs G, Neibecker D, Žarković N. Chemistry and personalized medicine - the research and development future of Europe. Croat Med J. 2012;53(4):291-293.
27. 2Rej R. Clinical chemistry through Clinical Chemistry: a journal timeline. Clin Chem. 2004;50(12):2415-2458.
28. Wang A, Xiu X, Liu S, Qian Q, Wu S. Characteristics of Artificial Intelligence Clinical Trials in the Field of Healthcare: A Cross-Sectional Study on ClinicalTrials.gov. Int J Environ Res Public Health. 2022;19(20).
29. 2Busnatu Ș, Niculescu AG, Bolocan A, Petrescu GED, Păduraru DN, Năstasă I, et al. Clinical Applications of Artificial Intelligence-An Updated Overview. J Clin Med. 2022;11(8).
30. Bhatt A. Artificial intelligence in managing clinical trial design and conduct: Man and machine still on the learning curve? Perspect Clin Res. 2021;12(1):1-3.
31. Russ AL, Fairbanks RJ, Karsh BT, Militello LG, Saleem JJ, Wears RL. The science of human factors: separating

fact from fiction. BMJ Qual Saf. 2013;22(10):802-808.
32. Katz M, Bosworth HB. Behavioral sciences in clinical practice. Einstein (Sao Paulo). 2016;14(1):vii-xiv.
33. Gillies K, Brehaut J, Coffey T, Duncan EM, Francis JJ, Hey SP, et al. How can behavioural science help us design better trials? Trials. 2021;22(1):882.
34. Kwizera R, Mande E, Omali D, Okurut S, Nabweyambo S, Nabatanzi R, et al. Translational research in Uganda: linking basic science to bedside medicine in a resource limited setting. Journal of Translational Medicine. 2021;19(1):76.
35. 3Meina L, Wenya Y, Feng Y, Tao D, Lulu Z. Awareness of and attitudes toward translational medicine among health personnel in hospitals in Shanghai, China. J Int Med Res. 2019;47(1):438-452.
36. Austin CP. Opportunities and challenges in translational science. Clinical and Translational Science. 2021;14(5):1629-1647.
37. 3Vukotich CJ, editor Challenges of T3 and T4 Translational Research | Vukotich, Jr. | Journal of Research Practice2016.
38. Blumberg RS, Dittel B, Hafler D, von Herrath M, Nestle FO. Unraveling the autoimmune translational research process layer by layer. Nat Med. 2012;18(1):35-41.
39. Faggion CM, Jr. The (in)adequacy of translational research in dentistry. Eur J Oral Sci. 2020;128(2):103-9.
40. Davidson A. Translational research: what does it mean? Anesthesiology. 2011;115(5):909-11.
41. Westfall JM, Mold J, Fagnan L. Practice-based research--"Blue Highways" on the NIH roadmap. Jama. 2007;297(4):403-6.
42. Barkhordarian A, Pellionisz P, Dousti M, Lam V, Gleason L, Dousti M, et al. Assessment of risk of bias in translational science. Journal of Translational Medicine. 2013;11(1):184.
43. Rubio DM, Schoenbaum EE, Lee LS, Schteingart DE, Marantz PR, Anderson KE, et al. Defining translational research: implications for training. Acad Med. 2010;85(3):470-5.
44. Domecq JP, Prutsky G, Elraiyah T, Wang Z, Nabhan M, Shippee N, et al. Patient engagement in research: a systematic review. BMC Health Serv Res. 2014;14:89.
45. Boenink M, van der Scheer L, Garcia E, van der Burg S. Giving Voice to Patients: Developing a Discussion Method to Involve Patients in Translational Research. Nanoethics. 2018;12(3):181-97.
46. Nakao K. Translational science: Newly emerging science in biology and medicine - Lessons from translational research on the natriuretic peptide family and leptin. Proc Jpn Acad Ser B Phys Biol Sci. 2019;95(9):538-67.
47. Manohar PR. The Translational Framework of Ayurveda as a Knowledge System. Anc Sci Life. 2016;36(2):59-60.
48. Ioachimescu OC. Medicinae investigationis, quo vadis? J Investig Med. 2021;69(1):2-3.
49. Wichman C, Smith LM, Yu F. A framework for clinical and translational research in the era of rigor and reproducibility. J Clin Transl Sci. 2020;5(1):e31.
50. Kahn K, Ryan G, Beckett M, Taylor S, Berrebi C, Cho M, et al. Bridging the gap between basic science and clinical practice: a role for community clinicians. Implement Sci. 2011;6:34.
51. Zarbin M. What Constitutes Translational Research? Implications for the Scope of Translational Vision Science and Technology. Transl Vis Sci Technol. 2020;9(8):22.
52. Homolak J. Opportunities and risks of ChatGPT in medicine, science, and academic publishing: a modern Promethean dilemma. Croat Med J. 2023;64(1):1-3.

53. Sallam M. ChatGPT Utility in Healthcare Education, Research, and Practice: Systematic Review on the Promising Perspectives and Valid Concerns. Healthcare (Basel). 2023;11(6).
54. Khan RA, Jawaid M, Khan AR, Sajjad M. ChatGPT - Reshaping medical education and clinical management. Pak J Med Sci. 2023;39(2):605-7.
55. Xue VW, Lei P, Cho WC. The potential impact of ChatGPT in clinical and translational medicine. Clin Transl Med. 2023;13(3):e1216.
56. Wen J, Wang W. The future of ChatGPT in academic research and publishing: A commentary for clinical and translational medicine. Clin Transl Med. 2023;13(3):e1207.
57. Kim SG. Using ChatGPT for language editing in scientific articles. Maxillofac Plast Reconstr Surg. 2023;45(1):13.
58. Agrawal P, Nikhade P. Artificial Intelligence in Dentistry: Past, Present, and Future. Cureus. 2022;14(7):e27405.
59. Quazi S. Artificial intelligence and machine learning in precision and genomic medicine. Medical Oncology. 2022;39(8):120.
60. Finkelstein J, Zhang F, Levitin SA, Cappelli D. Using big data to promote precision oral health in the context of a learning healthcare system. J Public Health Dent. 2020;80 Suppl 1(Suppl 1):S43-s58.
61. Fischer AH, Jacobson KA, Rose J, Zeller R. Hematoxylin and eosin staining of tissue and cell sections. CSH Protoc. 2008;2008:pdb.prot4986.
62. Lahiani A, Klaiman E, Grimm O. Enabling Histopathological Annotations on Immunofluorescent Images through Virtualization of Hematoxylin and Eosin. J Pathol Inform. 2018;9:1.
63. Chan JK. The wonderful colors of the hematoxylin-eosin stain in diagnostic surgical pathology. Int J Surg Pathol. 2014;22(1):12-32.
64. Goetz LH, Schork NJ. Personalized medicine: motivation, challenges, and progress. Fertil Steril. 2018;109(6):952-63.
65. Delpierre C, Lefèvre T. Precision and personalized medicine: What their current definition says and silences about the model of health they promote. Implication for the development of personalized health. Front Sociol. 2023;8:1112159.
66. Strianese O, Rizzo F, Ciccarelli M, Galasso G, D'Agostino Y, Salvati A, et al. Precision and Personalized Medicine: How Genomic Approach Improves the Management of Cardiovascular and Neurodegenerative Disease. Genes (Basel). 2020;11(7).
67. Yuan B. What Personalized Medicine Humans Need and Way to It --also on the Practical Significance and Scientific Limitations of Precision Medicine. Pharmgenomics Pers Med. 2022;15:927-42.
68. Almabadi ES, Bauman A, Akhter R, Gugusheff J, Van Buskirk J, Sankey M, et al. The Effect of a Personalized Oral Health Education Program on Periodontal Health in an At-Risk Population: A Randomized Controlled Trial. Int J Environ Res Public Health. 2021;18(2).
69. Amato A. Personalized Oral and Dental Care. J Pers Med. 2023;13(1).
70. Reddy MS, Shetty SR, Vannala V. Embracing Personalized Medicine in Dentistry. J Pharm Bioallied Sci. 2019;11(Suppl 2):S92-s6.
71. 7Wingrove S. Why Personalized Oral Hygiene Technology Matters. Compend Contin Educ Dent. 2022;43(3):f1-f4.
72. Bărbulescu R, Ioan D, editors. Multi-scale and reduced modelling of biological systems. 2015 9th International Symposium on Advanced Topics in Electrical Engineering (ATEE); 2015 7-9 May 2015.
73. Walpole J, Papin JA, Peirce SM. Multiscale computational models of complex biological systems. Annu Rev Biomed Eng. 2013;15:137-54.

74. Najafi A, Bidkhori G, Bozorgmehr JH, Koch I, Masoudi-Nejad A. Genome scale modeling in systems biology: algorithms and resources. Curr Genomics. 2014;15(2):130-59.
75. Baroni de Carvalho R, Shick E, Dye BA. The One Health initiative and its importance to oral health. J Am Dent Assoc. 2023;154(3):187-90.
76. Williams L. One Health and dentistry. Gen Dent. 2015;63(5):20-2.
77. Linder D, Cardamone C, Cash SB, Castellot J, Kochevar D, Dhadwal S, et al. Development, implementation, and evaluation of a novel multidisciplinary one health course for university undergraduates. One Health. 2020;9:100121.
78. Morens DM, Breman JG, Calisher CH, Doherty PC, Hahn BH, Keusch GT, et al. The Origin of COVID-19 and Why It Matters. Am J Trop Med Hyg. 2020;103(3):955-9.
79. Alanagreh L, Alzoughool F, Atoum M. The Human Coronavirus Disease COVID-19: Its Origin, Characteristics, and Insights into Potential Drugs and Its Mechanisms. Pathogens. 2020;9(5).
80. Platto S, Xue T, Carafoli E. COVID19: an announced pandemic. Cell Death Dis. 2020;11(9):799.
81. Mahdy MAA, Younis W, Ewaida Z. An Overview of SARS-CoV-2 and Animal Infection. Front Vet Sci. 2020;7:596391.
82. Austin CP. Opportunities and challenges in translational science. Clin Transl Sci. 2021;14(5):1629-47.
83. Hostiuc S, Moldoveanu A, Dascălu MI, Unnthorsson R, Jóhannesson Ó I, Marcus I. Translational research-the need of a new bioethics approach. J Transl Med. 2016;14:16.
84. Adeola HA, Soyele OO, Adefuye AO, Jimoh SA, Butali A. Omics-based molecular techniques in oral pathology centred cancer: prospect and challenges in Africa. Cancer Cell Int. 2017;17:61.
85. Adeola HA, Adefuye A, Soyele O, Butali A. The dentist-scientist career pathway in Africa: opportunities and obstacles. Korean J Med Educ. 2018;30(3):189-98.
86. Farrugia P, Petrisor BA, Farrokhyar F, Bhandari M. Practical tips for surgical research: Research questions, hypotheses and objectives. Can J Surg. 2010;53(4):278-81.
87. Fandino W. Formulating a good research question: Pearls and pitfalls. Indian J Anaesth. 2019;63(8):611-6.
88. Hugo FN, Kassebaum NJ, Marcenes W, Bernabé E. Role of Dentistry in Global Health: Challenges and Research Priorities. J Dent Res. 2021;100(7):681-5.
89. Patrick DL, Lee RS, Nucci M, Grembowski D, Jolles CZ, Milgrom P. Reducing oral health disparities: a focus on social and cultural determinants. BMC Oral Health. 2006;6 Suppl 1(Suppl 1):S4.
90. Peres MA, Macpherson LMD, Weyant RJ, Daly B, Venturelli R, Mathur MR, et al. Oral diseases: a global public health challenge. Lancet. 2019;394(10194):249-60.
91. Petersen PE, Bourgeois D, Ogawa H, Estupinan-Day S, Ndiaye C. The global burden of oral diseases and risks to oral health. Bull World Health Organ. 2005;83(9):661-9.