Chapter

Implantogenomic: Conceptualizing Osseointegration Toward Personalized Dental Implant Therapy

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Abstract

The spectrum of patients' needs for dental implant treatment ranges between healthy individuals to those with complex diseases and compromised jaw bones. The aim of this review chapter is to introduce the application of personalized dental medicine to dental implant field as a therapeutic strategy that is best suited to individualized patient's genetic makeup "Implantogenomics" to enhance their longevity and clinical outcomes. The ultimate goal of personalized medicine and dentistry is tailoring targeted treatment to the patient's individual genetic makeup and having predictive outcomes. This approach will transfer the traditionally known "one size fits all" to an actionable model, tailoring therapy to individuals in a homogenous stratified group. In this review chapter, in analogy to pharmacogenomics, personalized dental implant and its implantogenomics concept have been proposed as a novel application of personalized dentistry. It is conceivable that the actionable model that integrates genomics and materiomics will accelerate the production of personalized implantable biomaterials and biomedical devices. Moreover, the convergence of multi-disciplines including biological sciences, material sciences, and computational tools may underpin the application of personalized dental implant therapy in the future. This approach will unleash the potential of advancing technologies to tailor dental implants targeting different subpopulations. Despite this optimistic goal, challengeable remains ahead of us where the conduction of well-directed scientific and clinical research is needed.

Keywords: osseointegration, personalized dental implant therapy, omics, materiomics, implantogenomics

1. Introduction

For more than 50 years, dental implants were employed for the treatment of patients who are both partly and wholly edentulous. This treatment modality has been shown to improve the quality of life of large populations and demonstrated to perform very well, clinically, functionally, and esthetically [1–3]. Osseointegration is an essential factor in the success rates of dental implant-supported prostheses. The first known use of the term "osseointegration" was in the 1970s when Branemark defined it as a "Direct structural and functional link between organized, live bone tissue and the surface of a load-carrying artificial implant at the resolution level of the light microscope" [4]. At the bone-implant interface, osteoinduction and osteoconduction events are necessary for osseointegration to occur. The biological

Term	Definition
Artificial intelligence (AI)	Specific machine learning algorithms, has the ability to make decisive interpretation of "big"-sized complex data and, hence, appears as the most effective tool for the analysis and understanding of multi-omics data for patient-specific observations and complex biological process
Biomaterialomics	Integration of multi-omics data and high-dimensional analysis with artificial intelligence (AI) tools throughout the entire pipeline of biomaterials development
Materiomics	Introducing an omics approach to biomaterials research where the convergence of materials science, biological science, and technological advancement (encompassing computational methods and experimental assays) hold the promise in the production of personalized implantable biomaterials and biomedical devices
OMICs	A field of study in biology ending in *-omics*, such as genomics, proteomics, transcriptomic, or metabolomics. The related suffix *-ome* is used to address the objects of study of such fields, such as the genome, proteome, transcriptome, or metabolome, respectively
Personalizing dental implant	The integration of multi-omics data and advanced biotechnologies to tailor biofunctionalized implant system; treating both healthy and compromised jaw bone with the same success and survival rates
Personalized Medicine	Personalized medicine is an evolving field that uses diagnostic tools to identify specific biological markers, often genetic, to help determine which medical treatments and procedures will be best for each patient
Systems biology	A holistic approach to deciphering the complexity of biologic systems. It is collaborative, integrating many scientific disciplines, including biology, computer science, engineering, bioinformatics, physics, and others, to predict how these systems change over time and under varying conditions, and to develop solutions to the world's most pressing health and environmental issues

Table 1.
Shows the main terminologies used throughout the review.

mechanisms defining the three concepts are known to be connected yet distinct from one another [5].

Although osseointegration was defined as a time-dependent healing process, whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved and maintained in bone during functional loading, osseointegration, a novel definition has emerged recently [6]. Albrektsson et al. defined "osseointegration as a foreign body reaction where interfacial bone is formed as a defense reaction to shield off the implant from tissues" [7]. Understanding both the old definition and the new one necessitate conceptualizing osseointegration beyond its definitions.

To achieve such goal, this review chapter proposed an actionable model integrating various fields. The convergence of scientific disciplines including advancements in molecular biology in terms of "multi-omics data," bioengineering in the term "materiomics and biomaterialomics," and proper computational tools that will hasten the production of personalized implantable medical devices. Thus, the formulation of this strategic approach is critical toward personalized dental implant as a target future therapeutics. Moreover, the introduction of osseointegration's new concept "implantogenomics" demonstrates patient-specific implants whereby reliable dental implant therapy is tailored based on the genetically unique individual. **Table 1** shows the main terms used throughout the review.

2. Synopsis of wound healing around dental implants

The process of osseointegration involves a cascade of complex physiological mechanisms similar to intramembranous ossification and direct fracture bone healing [8]. After an implant is inserted into an osteotomy site, immediately protein serum is adsorbed onto the implant surface and forms conditioning layer. It is well known that the characteristics of implant surface determine the biological and molecular profile of the adsorbed protein layer. At the micro-environment between bone and implant surface, cells interact with this layer rather than with the implant surface itself [9, 10].

The protein adsorption stage is followed by coordinating and sequentially overlapping biological events. These biological events include mesenchymal and non-mesenchymal cellular interactions (i.e., recruitment, attachment, proliferation, and differentiation), soluble proteins and growth factors secretions, osteogenic cells proliferation and differentiation, osteoid production and matrix calcification, and bone formation and remodeling [11–14].

The principal factors that regulate the biological events of endosseous wound healing are the cells dominating the osteotomy site. Cells populate each stage of the healing process and are found to coordinate and communicate with each other by producing a myriad of signaling molecules including; cytokines, chemokines, growth factors, extracellular matrix proteins, hormones, and ions, which orchestrated the osseous healing process at biointerface. The secretion of the signaling molecules is well controlled by the sequential activation of corresponding typical genes [14, 15]. In fact, the decisive underlying cellular and molecular mechanisms that regulated endosseous wound healing and osseointegration are yet to be fully understood [15, 16]. **Figure 1** summarizes the biological events and the cellular and molecular mechanism of osseointegration.

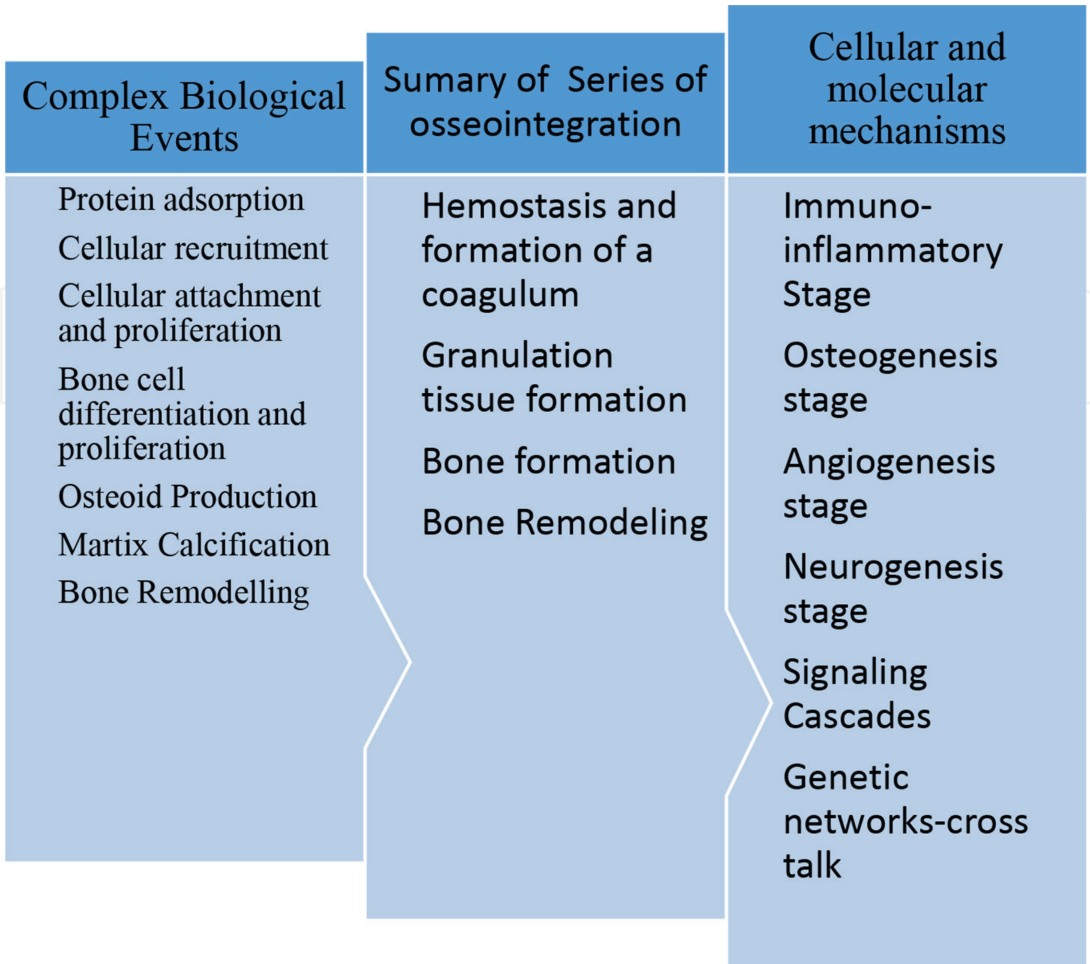

Figure 1.
Summary of the biological events and the cellular and molecular mechanisms of osseointegration.

3. Gene markers and genetic networks of osseointegration

The biological processes of osseointegration (inflammo-immuno-angio-neuro-osteogenesis processes) are directed by several genes expressed in an orderly sequence. Studies showed that gene expression profile after implant installation shifted from genes upregulated during immuno-inflammatory processes and cell proliferation to genes expression upregulated in favor of angiogenesis, osteogenesis, and neurogenesis processes [17, 18]. This alternation of biological processes may be attributed to the concept of "foreign body equilibrium." It has been proposed that osseointegration is the result of an immune system's reaction to a foreign body, which, at the right level of intensity, will balance itself out and allow osteogenesis to start on surface of the implant [19, 20].

Several in vitro and in vivo studies have demonstrated the influence of surface topography on gene expression of osseointegration. In brief, over the last two decades, the studies investigated the genetic basis of osseointegration have shown that the most observed genes were immunoinflammatory-related gene markers, extracellular matrix and osteoblast differentiation-related genes, bone formation, and remodeling-related genes, transcriptional-whole genome-proteome profiles of osseointegration related to immune-inflammo-angio-neuro-skeletogenesis biological processes, micro RNAs and signaling pathways. These biomarkers recapitulated the reported significant genetic markers and genetic networks associated with the biological processes of osseointegration [14, 16, 21–26].

Osseointegration encompasses a network of reactions that are dependent on a building system rather than a single pathway [20]. In this context, it is noteworthy that even though thorough studies have made significant progress in demonstrating the fundamental mechanisms underlying the molecular basis of osseointegration, as previously mentioned, the revolution of ongoing scientific research has highlighted the importance of other genetic networks related to osseointegration [25]. Whole genome microarray analyses have shown that the genetic networks that control osseointegration include other genes that function in coherent and/or independent pathways to complete the process of osseointegration around dental implants, in addition to the genes regulating osteogenesis and involving the expression of osteoblast marker genes. Other gene networks involved in the process of osseointegration include those that control the cross-linking of the bone collagen matrix, extracellular matrix-related genes associated with cartilage, and clock genes related to the peripheral circadian rhythm system. The modulation of those novel genetic networks was found to be topographical dependent and devoted to accelerate osseointegration [25, 27, 28].

4. The effect of implant surface properties on osseointegration

Implant surface properties including its topographical, chemical, mechanical, and physical are considered to be one essential factor to promote and maintain osseointegration. Since the foundation of osseointegration phenomenon, many bioengineering techniques have been developed to modify dental implant surface characteristics. These modification techniques have been classified into subtractive and additive treatments. Subtractive treatments include machining, Sandblasting, acid etching, and laser ablation. Additive treatments include anodization, fluoride surface treatment, nanoscale surface, plasma spraying, hydroxyapatite coating, electrophoretic deposition, biomimetic precipitation "peptides growth factors and ECM proteins", and drugs incorporated "bisphosphonates and statins" [29–33].

Recent reviews have shown that dental implant surface modifications were enormously studied aiming to promote osseointegration in the last decades [16, 26]. Mechanistically, implant surface properties are able to modulate osseous healing by influencing the cells-implant interactions and then producing several genes and proteins that serve as key regulators to inflammo-immuno-angio-neuro-osteogenesis processes [16, 26, 34].

Quit recently, new interesting approach is surface loading with cells potentially gaining more attention in the future [35]. However, this type of functionalization has not been extensively studied, as its clinical translation is more challenging due to the cell preparatory requirements and regulations. In tandem with the progression of cell-based therapy and personalized medicine, this approach may accelerate tissue repair in many clinical aspects [35].

5. Personalized medicine and dentistry

5.1 Personalized medicine

Personalized medicine is a contemporary evolving field in medicine and healthcare industries [36, 37]. Its aspirational goal is about tailoring medical treatment to the patient's individual genomic, anatomical, and physiological characteristics in order to provide a better quality of life and prolong life expectancy. Though the concept of current personalized medicine as new medical innovation was laid in tandem with the successful completion of the Human Genome Project (HGP) in the USA, in 2003 [37, 38], the term personalized medicine was coined in the published works in 1999 [39]. **Figure 2** shows the main elements of personalized medicine and dentistry concept.

The Human Genome Project (HGP) along with further projects (International HapMap Project (2002–2010), and the 1000 Genomes Project (2008–2015) authorizing personalized medicine to grow steadily in the medical practice and pharmacotherapy [37]. Among the main project achievements were discovering 1800 disease-related genes, developing numerous molecule biomarker-based tests, identifying genetic variations which lead to an individual different response to environmental factors, as well as drugs and vaccines effectiveness [37, 38, 40–42]. Personalized medicine has been extensively reviewed in the pharmacogenetics "study of genetic causes of individual variations in drug response" and pharmacogenomics (impact of multiple mutations in the entire genome that may determine the patient's response to drug therapy [43, 44].

Both pharmacogenetics and pharmacogenomics testing is involved as novel approaches in drug development and future registered therapeutic for a specific disease. For example, the implication of using pharmacogenetics and pharmacogenomics in the fields of cardiovascular, pulmonary, oncological, and bone diseases and also feature the potential economic value of their development [44, 45].

For centuries, health care providers, namely physicians treated medical conditions based on identifying the signs and symptoms and prescribed drug therapy without a diagnostic pretest. This traditional approach is so-called "One Size-Fits-Alls," which is doomed to failure. The failure has been attributed to several factors including lack of patient stratification, existing of genetic variation and treatment drug reaction, identifying risk assessment, understanding factors involved in disease development

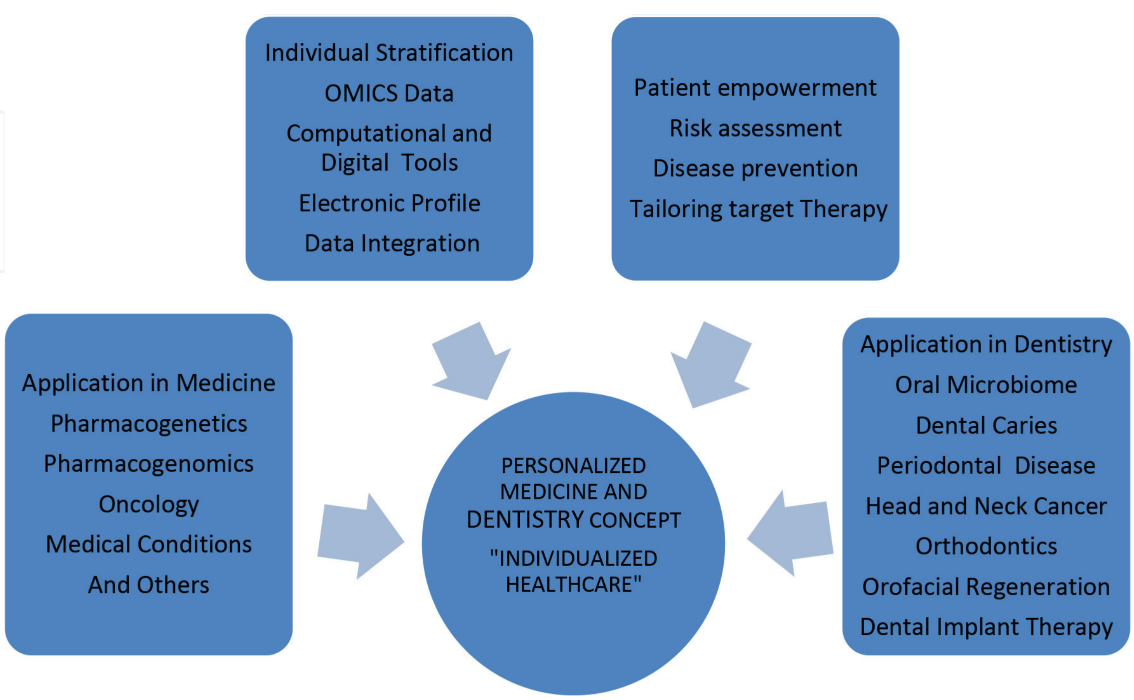

Figure 2.
Personalized medicine and dentistry concept: Main components and its applications in medical and dental fields.

"epigenetics" and taking in account patient's profile "age, sex and weight" [36, 37]. Collectively, such factors are the reason for extensive differences in response to medication.

The employing of pharmacogenetics and pharmacogenomics testing in personalized medicine will show which medication will have a positive effect and which one will have a negative effect. This approach will shift the paradigm from currently using "one size fits all" to individualizing drug target "a test and treat" approach. The consequence of such transformation is expanding the personalized medicine concept in the medical practice and healthcare industries [37, 46, 47].

Although there is no one uniform definition of personalized medicine because of lack of consensus on definitions and nomenclature, several agencies, institutes, and associations have provided a diverse range of definitions depending on the scope and the main elements of personalized medicine [37, 43]. Personalized medicine is a multifarious approach to patient care that not only improves our ability to diagnose and treat disease, but offers the potential to detect disease at an earlier stage, when it is easier to treat effectively. The full implementation of personalized medicine encompasses six domains (**Table 2**) [48].

The concept of personalized medicine [49] has been designated by many names in the literature [37, 50]; including precision medicine [51, 52], individualized medicine [53], network medicine [54], predictive medicine [55], stratified medicine [56] as well as P4 medicine [57]. These terms have a similar meaning with some slight differences between them and used interchangeably as alternative and synonyms terms [37, 50].

5.2 Personalized dentistry

Like medicine, there is a growing attention toward personalized/precision dentistry. The personalized dentistry branches from personalized medicine as an emerging concept, a multifaceted, individualized data-driven approach to oro-cranio-facial care environment. The personalized dentistry will act as an actionable model in dentistry that represents a paradigm shift in dental practice from the one size fits all approach to tailoring therapy to individuals in a homogenous stratified group. Each group of individuals sharing similar risk factor data includes but is not limited to genomic, environmental, e-health record, and lifestyle [50, 58–62].

Domain	Goal
1. Risk Assessment	Genetic testing to reveal predisposition to disease
2. Prevention	Behavior/lifestyle/treatment intervention to prevent disease
3. Detection	Early detection of disease at the molecular level
4. Diagnosis	Accurate disease diagnosis enabling individualized treatment strategy
5. Treatment	Improved outcomes through targeted treatments and reduced side effects
6. Management	Active monitoring of treatment response and disease progression

Table 2.
Domains of personalized medicine adapted from Reference [48].

Nowadays, the advances in personalized oral health focus on the creation of new digital technologies and medical devices, conceptualizing complex process align with understanding system biology, improving patient's stratifications, identifying biomarkers as diagnostic and prognostic factors related to disease development and progression. In to aforementioned, personalized oral health concentrates on developing proper treatment planning and early disease detection as preventive strategies. In fact, the main goal of personalized dental medicine is tailoring treatment taking into account its application, dosing, and response to treatment according to individual characteristics [50, 63, 64].

Bartold explained the importance of implementing personalized dentistry as a custom dental management model for the future of dental practice in two folds. First, this approach will bring the field of dentistry in tandem with current medical practice. Second, personalized dentistry stressing on patient-centered care and improving patient health outcomes [65].

In the last decade, several researchers have been investigating the application of personalized dentistry concept to various branches of dentistry. Some examples of these studies include, head and neck cancer [66, 67], periodontics [68–70], restorative [71–73], pedodontic [74–76], orthodontic [77, 78], TMJD [79], Public health and preventive care [80–84], prosthodontic [85], dental implant [16, 86–88], and oral rehabilitation and regenerative medicine [89].

In the context of advanced healthcare research in the medical field, personalized medicine is escalating, whereas, in dentistry, personalized dentistry is still in its infancy. Several challenges have been attributed to delay implementations of personalized dentistry in the practice environment. According to Polverini, these challenges include gaps in education of the current knowledge related to the basis of personalized dental medicine, addressing issues such as reimbursement for preventive dental procedures, insufficient an integrated electronic health record, difficulty in protecting patient genetic information, and differences in access to genomic medicine by certain populations. However, the dental profession should act in tandem with medical profession to pace toward innovation and harness advanced technologies to ensure the development and progression of personalized healthcare environment [62, 90].

6. Personalized dental implant therapy: Introducing Implantogenomics Concept

The emergence of advanced technologies underpins the application of personalized dental implant therapy as a novel dental approach to providing precise patient's care. In fact, the presence of a broad spectrum of patients with various conditions include systemic diseases, special needs, and syndromic and elderly with compromised jaws necessitate patient's stratifications who share similar risk factors. Having such homogeneous groups and subgroups will help in developing proper protocol, treatment decision and prediction and tailoring precise patient-centered treatment strategy.

In 2020, we have proposed the personalized dental implant along with its new concept implantogenomics [16]. The current opinion review wishes to introduce the new concept to more audience in both medical and dental fields. In analogy to pharmacogenomics, implantogenomics should accurately achieve three major components prior to be implemented as a future personalized therapeutic strategy in the realm of implantology. First, stratifying individuals into subgroups based on a person's unique genome, second, identifying specified prognostic and predictive biomarkers which characterized endosseous wound healing of each subpopulations, and third, applying genomic information to design dental implant suit each subpopulation.

It is conceivable that the actionable model which integrates multiple advancement technologies will leverage the development of new medical devices including dental implants in favor of regenerative medicine and dentistry. These include but is not limited to multi-omics data, advanced material science, biotechnologies, and contemporary bioinformatics tools along with artificial intelligence. It is suggested that the joining of bioinformatics and artificial intelligence will handle high throughput genetic data more precisely in terms of defining, categorizing and analyzing [91, 92]. The ultimate goal of personalized dental implant therapy is to have the four Rights. (1) Right treatment in terms of implant design and legitimate protocols, (2) Right patient in terms of patient stratification and minimal biological complication outcomes, (3) Right time in terms of bio-physiological events, and (4) Right Positioning in terms of Jaw status. **Figure 3** elucidates an actionable model of personalized dental implant therapy.

More recently, Albrektsson et al. proposed that personalized dental implant therapy and its implantogenomics concept may accelerate the development of genetic diagnostic tests as a target future therapeutic for residual ridge resorption (RRR) in elderly [16, 93]. In this regard, it should be mentioned that the application of personalized dental medicine to the realm of dental implant requires innovative leadership to direct wide-spectrum of scientific and clinical research as well as multidisciplinary and multicenter collaborations. Thus, the application of personalized dental medicine in the field of dental implant remains challengeable.

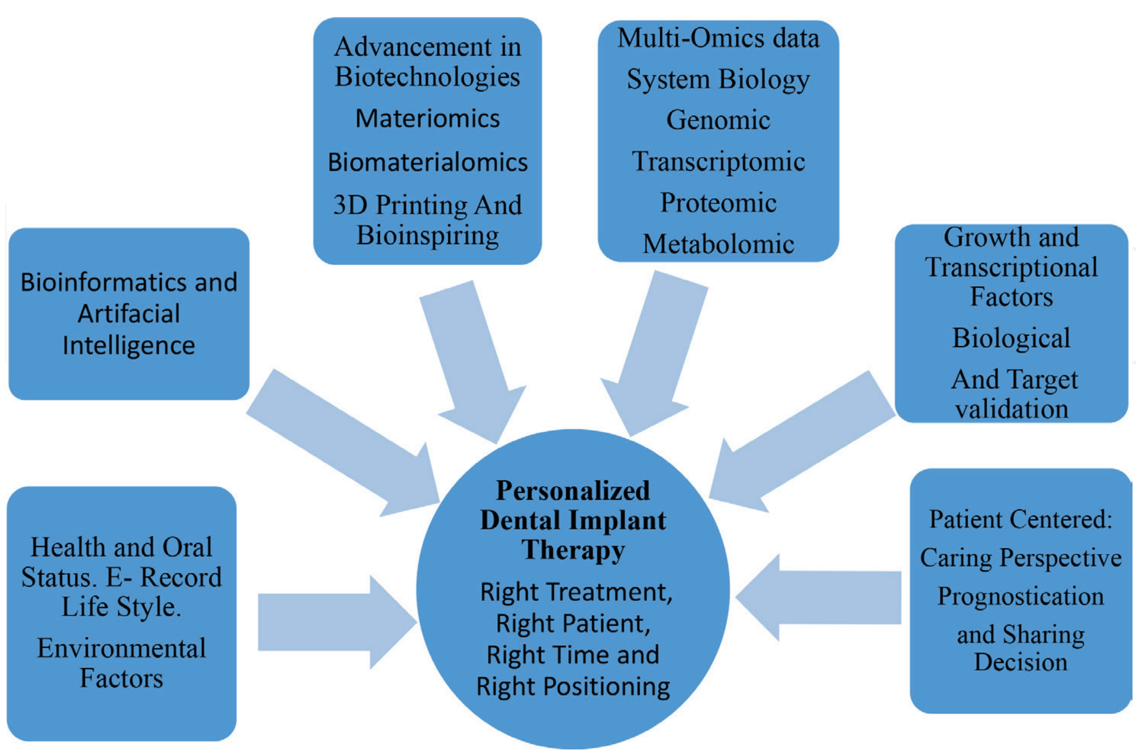

Figure 3.
An actionable model. The personalized dental implant therapy- the convergence of multiple disciplines.

7. Conclusions

The Integration of multi-disciplines including biological sciences, material sciences, and computational tools in actionable model may underpin the application of personalized dental implant therapy in the future. This approach will unleash the potential of advancing technologies to tailor dental implants targeting different subpopulations with more predictive outcomes. Despite this optimistic goal, challengeable remain ahead of us where conduction of well-directed scientific and clinical research is needed.

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