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# Emerging Insight Into- "Precision Periodontics"

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**Abstract**

*The longevity of people has increased globally along with an increase in comorbidities and medically compromised conditions. Periodontitis is among the most common health conditions that cause a major public health-related issue. With increasing prevalence, it has negative socio-economic impacts. Periodontitis-associated low-grade systemic inflammation shares the same pathological interplay with the systemic conditions that additionally raises awareness on the necessity for highly specific strategies for the prevention and management of periodontitis. Periodontal diagnosis is the backbone of a successful periodontal strategy since prevention and treatment plans depend on the accuracy and precision of the respective diagnostics.*

*Periodontal diagnostics is still based on conventional, clinical (pocket depth, clinical attachment loss, mobility) and radiological parameters (alveolar bone loss) that provide limited therapeutic guidance due to the multifactorial complexity of periodontal pathology, that is why biomarkers have been introduced in the new classification of periodontal and peri-implant conditions, 2017 as a pioneering step towards precision periodontics. Precision medicine is represented by biomarkers with the confluence of genomics, bioinformatics and digital technology. With the lack of periodontal markers validated for diagnostic use, the implementation of a precision medicine approach in periodontology remains in the very initial stage. This review aims to elaborate on the foundations of individualized therapy meeting the diagnostic needs in periodontal diagnostics, the concept of precision periodontics, periodontal biomarkers, with future implementation of a precision medicine approach in periodontal practice.*

## Introduction

With constant population growth and increased human lifespan, oral health strategies that have massively decreased the rate of tooth loss have expectedly resulted in an outbreak of periodontal diseases. Periodontitis represents a major public health problem. According to the Global Burden of Disease Study (2016), severe periodontal disease was the 11th most prevalent condition in the world.**[**1**]** The prevalence of periodontal disease was reported to range from 20% to 50% around the world.**[**2**]** It is one of the major causes of tooth loss which can compromise mastication, esthetics, self-confidence, and quality of life.**[**3,4**]** Hence, an immense efforts are made in the improvement of periodontal strategies for prevention and treatment, having their objective to minimize errors in diagnosis, improve outcomes, and avoid its negative socio-economic impacts with reduction in global periodontal burden. Diagnosis represents the backbone of successful periodontal treatment since the entire treatment plan, prognosis, and maintenance directly depends on the quality and precision of periodontal diagnosis. The crucial importance of accurate periodontal diagnostics extends far beyond clinical practice. Since periodontal diagnostics is still based on clinical and radiological parameters providing limited therapeutic guidance, the use of biomarkers has been introduced in the new classification of periodontal and peri-implant conditions, 2017 as a pioneer step towards the implementation of precision medicine concepts in periodontology.**[**5**]**

Precision medicine is a targeted treatment to a patient's specific needs on the basis of genetic, biomarker, epigenetic, phenotypic, and socioeconomic or psychosocial determinants that distinguish an individual from others with similar clinical presentations. Unfortunately, there is no validated biomarker for diagnostic use in periodontology, and since biomarkers are the driving force of precision medicine, the

implementation of a precision medicine in periodontics has been delayed. This review aims to elaborate the foundations of individualized therapy meeting the diagnostic needs in periodontal diagnostics, the concept of precision periodontics, periodontal biomarkers, with future implementation of a precision medicine approach in periodontal practice.

## What is Precision Medicine- A brief Insight

The National Research Council's Toward Precision Medicine **[**6**]** adopted the definition of precision medicine from the President's Council of Advisors on Science and Technology in 2008 as: "The tailoring of medical treatment to the individual characteristics of each patient…to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not". As the definition suggests, the power of precision medicine lies in its ability to guide health care decisions toward the most effective treatment for a given patient, and thus, improve care quality, while reducing the need for unnecessary diagnostic testing and therapies.

## Historical Significance

•Eighteen years ago, the Human Genome Project completed the first draft of the 3 billion base pairs (i.e., A, C, T and G nucleotides or bases) that make up a person's genomic DNA, that took a decade and nearly $300 million to complete a single person's genome.**[**7,8**]**

•By 2013, sequencing a patient's genome with annotation could be accomplished in less than a day for less than $1000 per genome.**[**9**]**

•In 2015, U.S. President Barack Obama stated an amount of $215 million to the "Precision Medicine Initiative" of the United States National Institutes of Health.**[**10**]** A short-term goal of the Precision Medicine Initiative was to expand cancer genomics to develop better prevention and treatment methods. In the long term, the Precision Medicine Initiative aimed to build a comprehensive scientific knowledge base by creating a national network of scientists and embarking on a national cohort study of one million Americans to expand our understanding of health and disease.

The Mission Statement of the Precision Medicine Initiative read: "To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized treatments". In 2016 this initiative was renamed "All of Us" and an initial pilot project had enrolled about 10,000 people by January 2018.**[**11**]**

## Components of Precision medicine:

A precision medicine ecosystem ideally links patients, clinicians, clinical laboratories and researchers. Researchers generate new findings from the data derived from samples linked to digital phenotypes, family history and environmental exposures all captured as part of clinical care. Clinicians utilize a growing knowledge base curated from clinical laboratories.

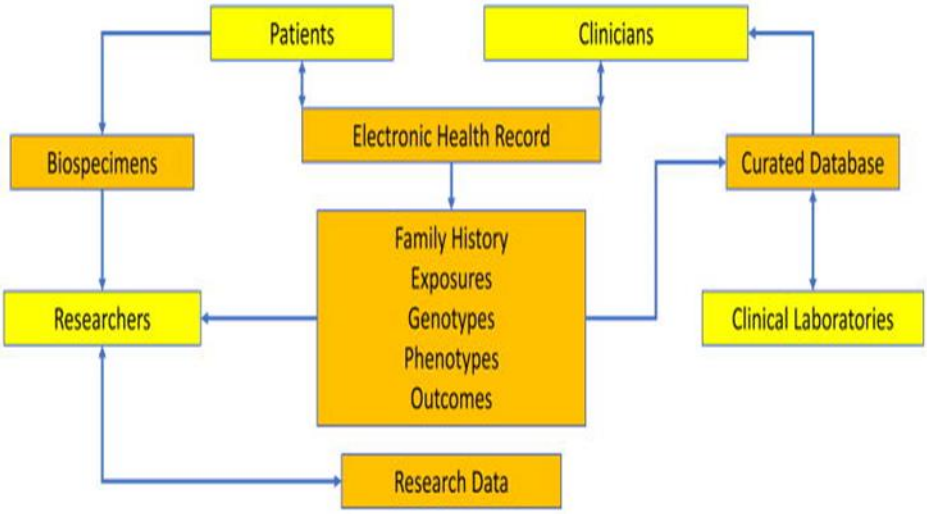



Figure 1. The Precision Medicine Ecosystem

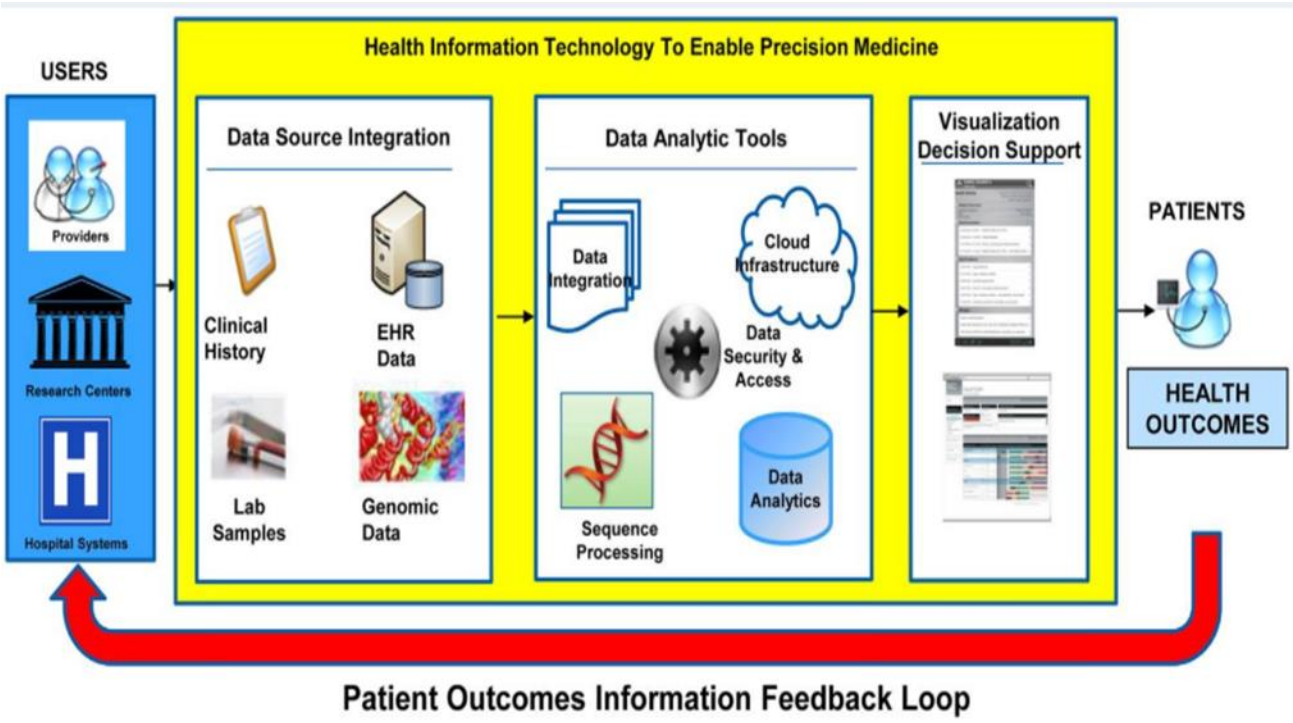



Figure 2. Bio-informatic technology role in Precision medicine

## Limitation of Conventional Periodontal diagnostic techniques:

a) Clinical and radiological measurements of attachment loss are not precisely accurate

b) Full mouth recording is necessary because of the site-specific nature of periodontal disease progression.

c) Individual susceptibility to periodontitis varies both genetically and over time

d) All clinical diagnostic techniques provide information about past disease activity and are unable to diagnose present disease activity

Benefits of Precision Medicine over Conventional diagnostic techniques:

a) Customize disease-prevention strategies

b) Prescribe more effective drugs

c) Avoid prescribing drugs with predictable negative side effects

d) Reduce the time, cost, and failure rate of pharmaceutical clinical trials

e) Eliminate trial-and-error inefficiencies that inflate health care costs and undermine patient care

f) Shift the emphasis in medicine from reaction to prevention

g) Predict susceptibility to disease

h) Improve disease detection

## Challenges In Periodontal Diagnosis

Periodontitis is a chronic multifactorial inflammatory disease triggered by dysbiotic biofilms leading to periodontal tissue destruction, clinically manifest as gingival bleeding, periodontal pocketing, clinical attachment loss (CAL), radiological signs of alveolar bone loss and mobility **[**12**]** Technological progress in biomedicine, including highly sensitive diagnostic techniques, and machine learning algorithms, together with tremendous progress in periodontal research, has completely changed the face of periodontal pathogenesis and clearly revealed the limitations of the standard clinical approach in providing highly reliable and patient specific diagnostic information.

- Periopathogen-centered theories have been replaced by the key-stone pathogen hypothesis of periodontal disease, depicting the dysbiotic changes within the periodontal microbiome triggered by key-stone periopathogens, rather than individual periopathogens.**[**13,14**]**

- The withdrawal of aggressive periodontitis concept from the new classification system of periodontal disease is the best example, since highly sensitive molecular methods demonstrated that Aggreggatibacter actinomycetemcomitans, initially considered a form-specific pathogen, was present in less than 50% of aggressive periodontitis cases and showed a similar distribution between healthy and diseased patients.
- With advancement in biofilm research, the complexity of biofilm structures have been revealed, the most prominent discoveries with clinical relevance are the importance of targeting the primary and secondary colonizers within preventive strategies.
- Additionally, the interference between biofilm embedded bacteria with standard antimicrobial treatments and routine antibiograms has been demonstrated**[**15**]** emphasizing the need for anti-biofilm approaches and the use of advanced methods for microbial sensitivity, such as omics.
- The role of non-periodontal pro-inflammatory factors, announced an immunological dysbiosis as a critical determinant of periodontal diseases.**[**16**]** Currently it is established that dysbiotic biofilms remain necessary but not sufficient to trigger periodontal diseases, while reinforced interactions between a dysbiotic microbiome and dysregulated inflammation are a hallmark of periodontal disease.**[**17**]** This concept has facilitated the understanding, identification, and confirmation of periodontal risk factors, such as the impact of viral and fungal species, systemic conditions, oral bad habits, hormonal changes, aging, and many other factors relying on inflammatory processes and their respective roles in local immunological breakdown and the deterioration of periodontal conditions.**[**18**]**
- Finally, it is considered that the immunophenotype plays an important role in the severity of periodontitis**[**19**]**, since it is considered that individuals with an overreactive genetic predisposition excessively react even to small amounts of bacterial biofilms, and this is particularly associated with periodontitis Stage 3 (previously called severe periodontitis) affecting up to 20% of the population.**[**20**]** Standard treatment protocols often fails to arrest progressive periodontal destruction as in Stage 3 periodontitis, while such patients exhibits low-grade systemic inflammation.**[**21,22**]**

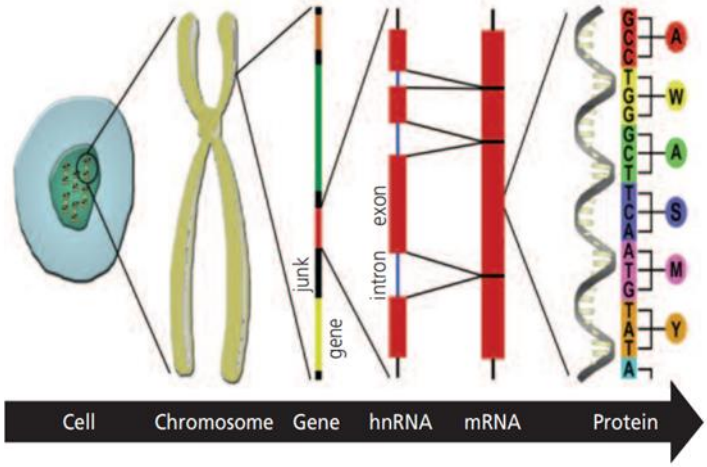
Considering these facts altogether, it is clear that the multifactorial complexity of periodontal pathology exceeds the capacity of a standard clinical diagnosis in providing accurate diagnosis and requires biomarker-supported diagnostics. Requirements in periodontal diagnostics and its related precision approach should be: predictors and markers for periodontitis onset; markers for staging and grading of disease, prognostic markers for the treatment outcome of periodontitis; prognostic markers for patient specific treatment.

## Precision Periodontics

Precision medicine is based on a combination of clinical parameters and biological markers reflecting the underlying biological processes; this enables highly reliable prediction of periodontal disease susceptibility, early diagnosis, prognosis, and planning of the most effective and safe treatment strategy meeting individual patient needs.**[**23**]** In vitro diagnostics (IVD) have set a breakthrough in this and accounts about 60% of all medical decisions today. IVD empowers clinicians to take decisions on highly specific and accurate diagnostic information and to customize a management strategy to fit individual patient needs.

## Biomarkers in Precision Medicine

A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention".**[**24**]** A biomarker is a substance used to indicate a biologic state and is an objective measure to evaluate the present and future disease activity. Various biological media like saliva, serum and gingival crevicular fluid are used to determine biomarkers in periodontal health and disease. A single biomarker will not able to predict periodontal disease activity and severity. So combinations of biomarkers are used to predict the disease activity.**[**25**]**




Thanks to advancement in 'OMICS' technologies including epigenomics, genomics, exomics, transcriptomics, proteomics, metabolomics, salivomics and nascent fields such as viromics coupled with bioinformatics and biostatistics, generated and processed massive biological data. The concept of biomarkers relies on the measurement of regulators or byproducts of the biological processes of interest, starting from the cellular level, through intercellular interactions, to complex interplay within the tissues, organs, and organic systems. Such a diagnostic concept provides objectively measurable diagnostic information on the target biological processes in real time, compensating most common

limitations of clinical parameters. With tremendous progress in biomedical technologies, practically any component of a biological process is measurable.

## Biomarkers in Periodontics

Biomarkers in periodontology can be classified based on the requested diagnostic information and based on the biological type appropriate for the clinical strategy in order to provide diagnostic information specific to each clinical phase.

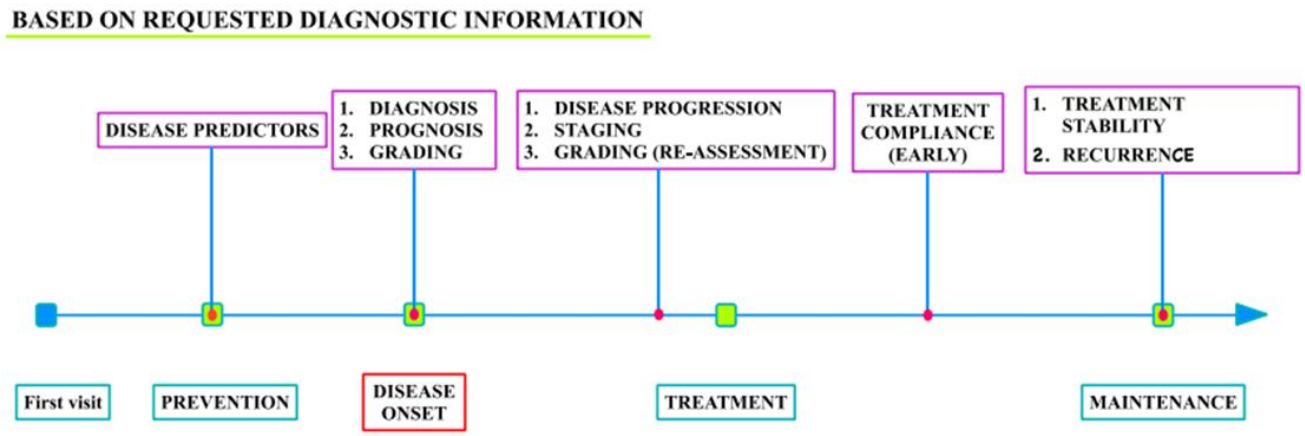



Figure 3. Biomarkers at various periodontal disease assessment and management stages

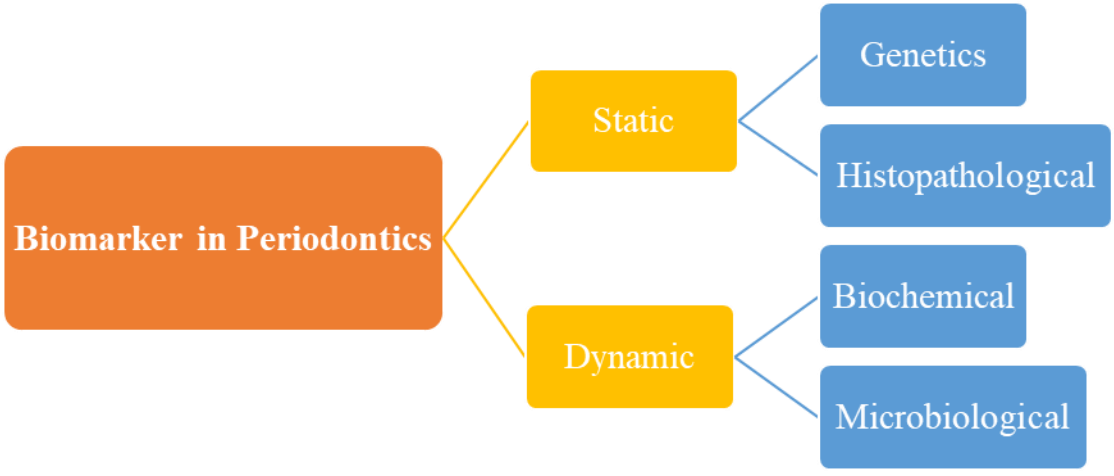



Figure 4. Biomarker in Periodontics based on Biological type

| Genetic biomarkers | Histopathological Biomarkers | Microbiological Biomarkers | Biochemical Biomarkers | Inflammatory Biomarkers |
|---|---|---|---|---|
| Cathepsin C gene<br>Mutation,<br>Collagen gene mutation,<br>IL-1 polymorphisms,<br>IL-10 polymorphisms,<br>Tumor necrosis factor,<br>Polymorphisms<br>Single neucleotide polymorphism (SNPs) | Not routinely used in periodontal diagnosis | Aggregatibacter actinomycetemcomitans,<br>Campylobacter rectus, Mycoplasmas,<br>Porphyromonas gingivalis,<br>Prevotella intermedia, Peptostreptococcus<br>Micros,<br>Prevotella nigrescens,<br>Treponema denticola,<br>Tannerella forsythia.<br>Treponema socransky | MMP-13, MMP-8, MMP-9, Cathepsin B, Gelatinase<br>Acid phosphatase,<br>Alkalinephosphatase, Aminopeptidase, Lactoferrin, Translactoferin,<br>αglucosidase,<br>Esterase, Elastase<br>Cystatins,<br>IgM, IgG, sIgA (secretory IgA)<br>Osteonectin, Osteocalcin, Osteopontin,<br>Platelet-activating factor, Epidermal growth factor, Platelet-derived growth factor,<br>Fibronectin, Trypsin, Vascular endothelial growth factor | IL-1β, IFNγ, and TNFα<br>IL-6, IL-4, and IL-10<br>RANKL/OPG |

Table 1. Shows list of biomarkers seen in periodontal disease

Biomarkers in periodontology can also be categorized as follows:

•Predictive markers measured in healthy individuals in the disease prevention stage;

•Diagnostic markers of disease onset;

•Prognostic markers for the assessment of disease progression, stage, and grade in the treatment planning phase

•Diagnostic markers and surrogate endpoints used to estimate patient compliance with the administered treatment, stability of the therapy results, and disease activity in the maintenance phase

Predictive markers are used before disease occurrence for the identification of risk factors and estimation of the overall patient risk, aiming at adjustment of the screening protocol and related modification of risk factors for optimal disease prevention. For this purpose, static markers are usually used; these do not change over time and are typically genetic markers. Single-nucleotide polymorphisms (SNPs) are certainly the most studied class of genetical markers in periodontology, presenting as variations in single basepair components of DNA that determine host responsiveness to environmental changes. Periodontal pathogens and/or to inflammatory overreaction to pathogens, resulting in excessive periodontal destruction. For this reason, the cytokines and immunoreceptors responsible for pathogen recognition remain in the spotlight of genetic studies. SNPs in IL-1β, IL1RN, FcYRIIIb, VDR and TLR4 genes may underline susceptibility to more destructive forms of periodontitis**[**26**]** while polymorphisms in the IL1β, IL1RN, IL6, IL10,VDR,CD14,TLR4 and MMP1 genes might be responsible for general susceptibility to chronic periodontitis.**[**27**]** However an extensive studies need to be done on large population to draw a conclusion.

Prognostic markers are measured when disease occurs; they do not need to change over time, and they serve to estimate disease characteristics, stage, and grade, which are indispensable for accurate prognostics of the progression pattern and responsiveness to different treatment protocols. The most frequently used are genetic markers. Therefore, prognostic markers should guide the clinician in the process of treatment planning to mitigate aggravating factors and minimize disease complications, in the selection of a suitable treatment protocol, and in setting the maintenance regimen for optimal treatment stability. IL-lα and IL-1β loci was associated with severe periodontitis.**[**28**]** IL1A and IL1B genetic variations are significant contributors to chronic periodontitis in Caucasians.**[**29**]** TNFα gene located on chromosome 6 within the major histocompatibility complex (MHC) gene cluster at the location 6p21.3 is associated with familial ability to produce higher or lower cytokine levels during periodontitis.**[**30**]**

Diagnostic markers comprise a wide group of indicators able to disclose disease onset, disease activity, and related disease progression, usually represented by fast-response biochemical and microbiological

markers. A specific subset of diagnostic markers includes surrogate endpoints intended for estimation of the patient's compliance to the administered treatment. These groups of biomarkers mostly comprise soluble inflammatory, soft tissue, and bone turnover markers (BTMs).[31] The inflammatory biomarkers in periodontology are represented by pro- and anti-inflammatory cytokines, host-derived enzymes, and markers of oxidative stress. Since these markers are elevated in both gingivitis and periodontitis, they are preferably used to estimate disease activity, progression, and compliance with administered treatment. Calprotectin inhibits immunoglobulin production and act as a proinflammatory protein. Increased expression of calprotectin at the site of inflammation offer protection against bacterial invasion to epithelial cells especially P.gingivalis.[32] Osteonectin plays a vital role in early phase of mineralization so it can act as a sensitive marker for detection of periodontitis. The sensitivity of this marker for diagnosing periodontal disease more when compare with N-propeptide of type I collagen.[33] Osteopontin helps in bone remodeling. In periodontitis, OPN levels are increased. There is a positive correlation between increased levels of OPN to probing pocket depth.[34,35] When nonsurgical periodontal treatment is provided GCF, OPN levels are significantly reduced.[36] Cathepsin-K, calprotectin, and osteocalcin also show a promising capacity for periodontitis diagnosis and predicting treatment outcomes.[37,38]

Soft tissue markers are used for monitoring soft tissue degradation and regeneration, and matrix metalloproteinases (MMPs) and growth factors are the most repurposed markers used in periodontology. Increased levels of MMP-8 are signifying conversion of gingivitis into periodontitis. No associations are found between MMP-8 levels and bone loss.[39] It is found that 18-fold increase of MMP-8 in patients experiencing active periodontal tissue breakdown as compared with patients under stable condition.[40] MMP-9 levels is reported in patients with recurrent attachment loss.[41] MMP-9 in oral diagnostics may best serve as a guide in periodontal treatment monitoring. Elevated levels of both MMP-13 and MMP-8 are correlate with irreversible peri-implant vertical bone loss around loosening dental implants.[33] In patients with untreated periodontal disease, collagenase present predominantly in the active form.[40] In the future, MMP-13 may be useful for diagnosing and monitoring the course of periodontal disease as well as tracking the efficacy of therapy. Platelet derived growth factor (PDGF) supports the healing. increased Vascular endothelial growth factor (VEGF) expression in epithelial cells and endothelial cells in periodontitis-affected gingiva could be an useful marker for periodontal disease. Elevated rate of salivary Epidermal growth factor (EGF) secretion in aggressive patients may be associated with the pathogenic mechanisms of aggressive periodontitis.[42]

Bone turn over markers (BTMs) are considered the most important markers in periodontology to indicate inflammatory osteoclastogenesis onset and activity within periodontitis onset and activity, respectively. The RANKL/OPG relative ratio was proposed as a promising marker of periodontitis onset, but its diagnostic value in the assessment of disease activity has not yet been established.[43]

Microbiological markers, the real-time polymerase chain reaction (RTPCR) assessment of Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, Fusobacterium nucleatum, Treponema denticola, and Campylobacter rectus provides the most accurate information about periodontitis, its progression[44] and its responsiveness to administered treatment[45] while the diagnostic value of Aggregatibacter actinomycetemcomitans currently remains controversial.

Histopathological markers are not routinely used in periodontal diagnosis, but they may provide important information regarding the disease's nature, pattern of progression, and grade and related to the validation of biomarkers most suitable for everyday use in the clinical setting.

## Precision Periodontics- Where are we now??

New technologies for comprehensive biological profiling of patients have initiated a switch to precision periodontics[46]; however, this remains in the very initial stage. As mentioned above, the driving forces of precision medicine are validated biomarkers and machine learning algorithms, and so far, in periodontology, there is no biomarker validated for diagnostic use, while algorithms are predominantly exploited in observational studies (regression methods and clustering analyses) and rarely for diagnostic purposes. The confusing aspect of the lack of diagnostic markers in periodontology and implantology[47], despite so many reported biomarker studies, relates to a frequent misinterpretation of biomarkers specifically validated for diagnostic use. Biomarker validation studies aim to identify promising candidate markers to answer specific clinical requests, to standardize pre-analytical protocols (sampling and storage) and analytical protocols (laboratorial methods), and to provide highly accur Some common reasons for the lack of diagnostic markers in periodontology can be summarized as follows: High interstudy variability in clinical diagnostic criteria and case definition; small sample sizes; inappropriate study designs regarding candidate marker selection for specific diagnostic needs, clinical strategy, and data processing; variability in specimen collection and storage protocols and data reporting. Biomarkers validated for diagnostic use need to have a highly reproducible diagnostics protocol with established accuracy, sensitivity, specificity, false positive rate, false negative rate, and diagnostic range precisely disclosed in the diagnostic information; so far, these kinds of diagnostic studies have been scarce in periodontology and implantology[44,48]

In context of microbiological markers, diagnostic focus should be directed to the assessment of a panel of key-stone periopathogens, together with opportunists; recognized as a crucial diagnostic indicator in distinguishing health from disease, disease progression, and responsiveness to the performed treatment. It is thus expected that metagenomic and metatranscriptomic methods, together with culturomics[49] will contribute to the identification of highly specific microbiological markers for accurate diagnosis and prognosis of periodontal disease. In the context of assessing quantitative changes, quantitative RT-PCR is the method of choice, while quantitative omics-based methods are in a stage of development as well.

In the context of biochemical markers, proteomics is an analytical method that can contribute to the identification of highly specific cytokine panels, and different multiplexing methods enable the assessment of a great range of protein profiles.[48] BTMs are fast-response markers that reflect the nature and volume of the ongoing bone processes, practically enabling the clinician to visualize the bone status at the molecular level, far before clinical/radiological manifestations; this is valuable for early diagnosis of the conversion of gingivitis into periodontitis, early assessment of patient compliance with the administered treatment, and diagnosis of possible recurrence during maintenance care. The advanced "omics" methods that can particularly contribute to the identification of new bone markers are metabolomics, particularly regarding identification of the byproducts of bone destruction for real-time assessment of changes in the bone level over time or in response to treatment.

Histopathological studies will contribute to biological definitions of the grading criteria of periodontitis. Finally, the entire process of biomarker validation directly depends on the quality of the clinical aspect of diagnostic studies. Hence, strict adherence to the clinical diagnostic criteria and case definitions defined in the referent classification of periodontal conditions is the ultimate precondition for accurate validation of periodontal biomarkers.

## Conclusion

Precision periodontics undoubtedly represents the future of high-quality periodontal care, so it is of paramount importance that future research studies strictly adhere to the recommendations for the validation of biomarkers in order to accelerate the process of their implementation in routine clinical practice. Future studies should focus on the development of biomarker assessment protocols applicable in everyday practice, such as point-of-care testing (POCT), which is still in the developmental stage in periodontology.[49,50] With the lack of periodontal markers validated for diagnostic use, the implementation of a precision medicine approach in periodontology remains in the very initial stage.

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