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Precision dental medicine for implant-supported oral rehabilitation: proposal of a prediction tool for the success of implants

Odontoestomatología de precisión para la rehabilitación oral implantosoportada: propuesta de una herramienta de predicción del éxito del implante

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Tesis doctoral
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PAPER 1

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PAPER 2

Bornes R, Montero J, Correia A, Marques T, Rosa N. Peri-implant diseases diagnosis, prognosis and dental implant monitoring: a narrative review of novel strategies and clinical impact. BMC Oral Health. 2023 Mar 30;23(1):183.

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III. ACRONYMS

PDM – Precision dental medicine

PM – Precision medicine

AI – Artificial intelligence

FMDUCP – Faculdade de Medicina Dentária da Universidade Católica Portuguesa

IDRA - Implant Disease Risk Assessment

IFPT – Implant failure predictive tool

PISF - Peri-implant sulcular fluid

GCF - Gingival crevicular fluid

PoC – Point-of-care

MMP-8 - Matrix metalloproteinase - 8

aMMP-8 – Active-matrix metalloproteinase - 8

Bop - Bleeding on probing

BL – Bone Level

PD – Probing depths

SPT – Supportive periodontal treatment

TNF-α - Tumor necrosis factor-α

IL-1β – Interleucina - 1β

TLR - Toll-like receptor

WHO – World health organization

FDA – Food and Drug Administration

NMR – Nuclear magnetic resonance spectroscopy

PCR – Polymerase chain reaction

GWAS – Genome-Wide Association Studies

DNA – Deoxyribonucleic acid

RNA – Ribonucleic acid

mRNA – Messenger ribonucleic acid

tRNA – Transfer RNA

miRNA – Micro RNA

IV. ABSTRACT

Background

The growth of population and of increased lifespan has meant that more people are looking for treatments and solutions for lost teeth, resulting in an increased demand for bone regeneration treatments and oral rehabilitation techniques for elderly patients with specific health conditions. Patient-related conditions, such as smoking habits, poor oral hygiene, infectious processes, systemic diseases (osteoporosis, diabetes mellitus…), and drugs that affect bone metabolism, might influence the progress of bone regeneration and, consequently, the osseointegration of dental implants. In addition, factors related to the surgical and prosthetic phase, as well as the inherent characteristics of dental implants. Therefore, information about the rehabilitation, including the implant system used, fixation method, and abutment used, is needed. Patient history and radiographic examination provide information that allows the clinician to identify the implant system. The development of methodologies able to integrate all the factors and predictors is possible with the use of artificial intelligence (AI). These strategies support the prognosis of the implant, predicting eventual clinical conditions such as early bone loss, mucositis, or periimplantitis.

The scientific evidence, as well as the assessment tools used in contemporary practice, has been based on clinical, analytical, and radiographic parameters which provide the clinician with limited therapeutic guidelines to deal with the multifactorial complexity of the implantsupported rehabilitation procedures. Furthermore, for diagnosing and staging peri-implant disease, such methods can only register the actual tissue destruction rather

than current disease activity. Moreover, those conventional strategies do not consider systemic conditions, which may influence the local immunological response, either around a tooth area (periodontitis) or around a dental implant area (peri-implantitis). Currently, the role of pathogens and their influence on periodontal and peri-implant diseases have been well described and it has been reported that oral dysbiotic status is necessary to trigger these pathologies. This understanding has allowed the identification and confirmation of several individual conditions such as risk factors with immunological impact.

The Omics methodology (i.e. the term "omics" derives from the Greek word "omnis," meaning "all" or "complete," and is used to describe the holistic and systematic study of various biological components) is key to the introduction of precision medicine into dentistry, especially in the field of implant-supported oral rehabilitation, because it can adapt the procedure to follow considering the patient’s biological, social, and lifestyle characteristics. A major goal is to reduce diagnostic mistakes, to develop results, to avoid unnecessary collateral effects, and to clarify why one individual can develop peri-implantitis and others with similar conditions did not.

Objectives

This doctoral thesis aims to take the first steps towards the creation of a protocol to be followed in cases of implant-supported oral rehabilitation, which complies with the assumptions of precision medicine. Considering the aim and transversality of precision medicine, it is imperative to create protocols that aim to respond to its assumptions, ideally through the application of AI algorithms and omics methodologies such as biomarkers. The specific objectives of this thesis were: 1) to review the literature on bioinformatics (artificial intelligence and *omic* sciences), addressing the state of the art of how its have been used to predict the success of dental implants; 2) to review how the molecular point-of-care (PoC) tests currently available can help in the early detection of peri-implant diseases; 3) to identify a test kit commercially available and approved on European Union that are already been validated to function with peri-implantitis biomarkers and that use oral fluid to diagnose; 4) to investigate dentists' perception of the implementation of a tool to support peri-implant risk assessment; 5) to create a usability test to identify improvements that can be made to the IDRA tool and, 6) to create a proposal tool to predict the success of dental implants.

Methods

A bibliographic review was made in PubMed and Web of Science respecting the methodology described in the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist. The focal question was “how are bioinformatics being used in the field of oral implantology as a predictive tool to ensure implant success?”

A second search strategy was created to answer the question: “How the molecular point-of-care tests currently available can help in the early detection of peri-implant diseases and throws light on improvements in point of care diagnostics devices?” The methodology included applying a search strategy, defining inclusion and exclusion criteria, and retrieving studies; selecting studies; extract relevant data; and performing tables to summarize the results. Searches of PubMed and Web of Science were performed to gather literature published until September 2022.

A qualitative study was performed to explore dentists’ perceptions toward the implementation of a dental informatics risk assessment tool. The Implant Disease Risk Assessment Tool (IDRA) was presented to a convenience sample of seven dentists working in a university clinic, who were asked to use IDRA with the information of three clinical cases whilst thinking aloud and then fill the System Usability Scale (SUS). A semi-structured interview technique was used with audio record to allow free expression of participants' perceptions related to the IDRA. The interviews information was categorized and analyzed by the authors.

Results

In the first review, three articles discussed bioinformatic models that integrated AI algorithms into established identification and quantification protocols, which are often used in Omics sciences. A total of 13 articles underlined the development of different AI algorithms, for example, machine learning, deep learning, and convolutional neural network to support clinical decision and raising precision and accuracy levels of the rehabilitation process. Of these, 6 studies developed AI models for implant type recognition. Most of the articles identified used AI algorithms as a clinical support tool, as opposed to the articles which applied bioinformatic strategies by combining knowledge from AI algorithms with Omics expertise. The conventional criteria currently used as a technique for the diagnosis and monitoring of dental implants are insufficient and have low accuracy. Models that apply AI algorithms combined with precision methodologies and biomarkers are extremely useful in the creation of precision medicine, allowing medical dentists to forecast the success of the implant. Tools that integrate the different types of data, including imaging, molecular, risk factor, and implant characteristics, are needed to make a more accurate and personalized prediction of implant success.

At the second review it was found, the PerioSafe® PRO DRS (dentognostics GmbH, Jena) and ImplantSafe® DR (dentognostics GmbH, Jena) ORALyzer® test kits, already used clinically, can be a helpful adjunct tool in enhancing the diagnosis and prognosis of periodontal/peri-implantar diseases. With the advances of sensor technology, the biosensors can perform daily monitoring of dental implants or periodontal diseases, making contributions to personal healthcare and improve the current status quo of health management and human health. More and more emphasis is given to the role of biomarkers in diagnosing and monitoring periodontal and peri-implant diseases. By combining these strategies with traditional protocols, professionals could increase the accuracy of early detection of peri-implant and periodontal diseases, predicting disease progression, and monitoring of treatment outcomes.

Regarding the usability test of the IDRA tool, to our knowledge, this was the first study conducted to develop a qualitative usability test of IDRA, evaluating the effectiveness, efficiency, and users' satisfaction. There were more variations in responses the greater the degree of complexity of the clinical case. Generally, the participants classified the tool as good, getting usability values of 77,2 (SD 19,8) and learnability 73,2 (SD 24,5). Four additional factors should be considered to improve IDRA tool: 1) considering the relation between contour angle and peri-implant tissue height; 2) automatic periodontal classification in the IDRA tool after completing the periodontogram in the clinical software; 3) presentation of a flow chart to assist therapeutic decisions alongside the final score defined by the IDRA tool; 4) integrating of precision tests such as Implantsafe® DR (dentognostics gmbh, Jena) and Oralyzer®(dentognostics gmbh, Jena).

Etiology and pathogenesis of peri-implant diseases is multifactorial. These tools must follow a natural integration to be easily applied in a clinical setting. It is important to study their usability from the clinicians' point of view, evaluating the effectiveness, efficiency, and users' satisfaction.

Conclusions

Based on these findings, it is possible to create a proposal tool that will integrate the assumptions of precision medicine, incorporating updated strategies to support the diagnosis and predict the dental implant success. This proposal tool can be seen as an eventual update to IDRA, since it was mentioned by the authors that if additional factors become evident from the literature, modifications of the diagram may be appropriate.

The proposed tool created is called the Implant Failure Prediction Tool – IFPT. The IFPT is not yet translated into digital format, it only exists as a concept design.

Currently, this tool has all the conditions to be used to assist in the early diagnosis of peri-implant diseases, namely mucositis and peri-implantitis, through ImplantSafe® test kits. Its completion and risk calculation follows the same rationale of IDRA. However, to improve the doctor-patient communication and to make it easier for the patient to understand and follow up his/her own case, the result provided by the IFPT is given as traffic signal, besides the written indication of the risk of developing a peri-implant disease. Thus, from the patient's point of view, the greenish the diagram is, the more possibility of implant success patient has. If a yellow vector appears, it means that the patient should modulate his or her behavior to change it to the green level; the more reds appear in the diagram, the higher the risk of developing peri-implant disease.

In the foreseeable future, it will function as an individualized tool that will accurately predict the success of the dental implant. Currently, what is within our reach is to start creating a diagnostic and prognostic model. Defining a longitudinal study methodology that allows the loading of as many clinical cases as possible into the IFPT ("inputs") and, through the follow-up of these patients, to identify/diagnose possible clinical outcomes of peri-implantitis, mucositis or peri-implant health ("outcomes") over time. In this way, as the data are processed by means of IA algorithms, the variables/predictors with more significance for the determination of the implant failure may be identified and, at the same time, their respective weights in the predicting algorithm. This methodology will be detailed throughout the next topic of the discussion. This tool will use AI algorithms, namely artificial neural networks technology, allowing the tool to accumulate different functions as it is used. Artificial neural networks are highly flexible models and have been used in medicine to explore relationships between various physiological variables and to build predictive models. In this way it is possible to define an algorithm capable of indicating with accuracy and precision treatment response.

V. RESUMEN

Antecedentes

El crecimiento de la población y el aumento de la esperanza de vida han hecho que cada vez más personas busquen tratamientos y soluciones para la pérdida de piezas dentales, lo que se traduce en una mayor demanda de tratamientos de regeneración ósea y técnicas de rehabilitación oral para pacientes de edad avanzada con determinadas condiciones de salud. Las condiciones relacionadas con el paciente, como el hábito de fumar, una higiene bucal deficiente, procesos infecciosos, enfermedades sistémicas (osteoporosis, diabetes mellitus...) y fármacos que afectan al metabolismo óseo, podrían influir en el progreso de la regeneración ósea y, en consecuencia, en la osteointegración de los implantes dentales. Además, existen factores relacionados con la fase quirúrgica y protésica, así como con las características inherentes a los implantes dentales. Por lo tanto, se necesita información sobre la rehabilitación, incluido el sistema de implante utilizado, el método de fijación y el pilar utilizado. El historial del paciente y el examen radiográfico proporcionan información que permite al clínico identificar el sistema de implantes. El desarrollo de metodologías capaces de integrar todos los factores y predictores es posible con el uso de la inteligencia artificial (IA). Estas estrategias apoyan el pronóstico del implante, prediciendo eventuales condiciones clínicas como pérdida ósea precoz, mucositis o periimplantitis.

La evidencia científica, así como las herramientas de evaluación utilizadas en la práctica contemporánea, se han basado en parámetros clínicos, analíticos y radiográficos que proporcionan al clínico directrices terapéuticas limitadas para hacer frente a la complejidad multifactorial de los procedimientos de rehabilitación sobre implantes.

Además, para diagnosticar y ponderar la enfermedad periimplantaria, dichos métodos sólo pueden registrar la destrucción real del tejido y no la actividad actual de la enfermedad. Además, esas estrategias convencionales no tienen en cuenta las condiciones sistémicas, que pueden influir en la respuesta inmunológica local, ya sea alrededor de una zona dental (periodontitis) o alrededor de una zona de implante dental (periimplantitis). Actualmente, el papel de los patógenos y su influencia en las enfermedades periodontales y periimplantarias están bien descritos y se ha informado de que el estado disbiótico oral es necesario para desencadenar estas patologías. Esta comprensión ha permitido la identificación y confirmación de varios factores de riesgo individual con impacto inmunológico.

La metodología “ómica” ("ómica" proviene de la palabra griega "ómis", que significa "todo" o "completo") es clave para la introducción de la medicina de precisión en odontología, especialmente en el campo de la rehabilitación sobre implantes dentales, ya que puede personalizar el procedimento terapéutico teniendo en cuenta las características biológicas, sociales y de estilo de vida del paciente. Uno de los principales objetivos es reducir los errores de diagnóstico, desarrollar resultados, evitar efectos colaterales y aclarar por qué un individuo puede desarrollar periimplantitis y otros no en condiciones similares.

Objetivos

Esta tesis doctoral pretende dar los primeros pasos hacia la creación de un protocolo a seguir en casos de rehabilitación oral implanto-soportada, que cumpla con los supuestos de la medicina de precisión. Teniendo en cuenta la finalidad y transversalidad de la medicina de precisión, es imperativo crear protocolos que pretendan dar respuesta a sus supuestos, idealmente mediante la aplicación de algoritmos de IA y metodologías ómicas como los biomarcadores. Los objetivos específicos de esta tesis fueron: 1) revisar la literatura sobre bioinformática (inteligencia artificial y ciencias ómicas), abordando el estado del arte de cómo se han utilizado para predecir el éxito de los implantes dentales; 2) revisar cómo los test moleculares point-of-care (PoC) actualmente disponibles pueden ayudar en la detección precoz de enfermedades periimplantarias; 3) identificar un kit de pruebas disponible comercialmente y aprobado en la Unión Europea que ya haya sido validado para funcionar con biomarcadores de periimplantitis y que utilice fluidos orales para el diagnóstico; 4) investigar la percepción de los dentistas sobre la implementación de una herramienta para apoyar la evaluación del riesgo periimplantario; 5) crear una prueba de utilidad para identificar las mejoras que se pueden realizar en la herramienta IDRA y, 6) crear una propuesta de herramienta para predecir el éxito de los implantes dentales.

Métodos

Se realizó una revisión bibliográfica en PubMed y Web of Science respetando la metodología descrita en la lista de verificación Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). La pregunta central fue "¿cómo se está utilizando la bioinformática en el campo de la implantología oral como herramienta predictiva para asegurar el éxito de los implantes?".

Se creó una segunda estrategia de búsqueda para responder a la pregunta: "¿Cómo pueden ayudar las pruebas moleculares en el punto de atención actualmente disponibles en la detección precoz de enfermedades periimplantarias y arrojan luz sobre las mejoras en los dispositivos de diagnóstico en el punto de atención?". La metodología incluyó la aplicación de una estrategia de búsqueda, la definición de criterios de inclusión y exclusión, y la recuperación de estudios; la selección de estudios; la extracción de datos relevantes; y la realización de tablas para resumir los resultados. Se realizaron búsquedas en PubMed y Web of Science para recopilar la literatura publicada hasta septiembre de 2022.

Se realizó un estudio cualitativo para explorar las percepciones de los dentistas respecto a la aplicación de una herramienta informática de evaluación de riesgos odontológicos. Se presentó la Herramienta de Evaluación del Riesgo de la Enfermedad del Implante (IDRA) a una muestra de conveniencia de siete dentistas que trabajaban en una clínica universitaria, a los que se pidió que utilizaran IDRA con la información de tres casos clínicos mientras pensaban en voz alta y luego rellenaban la Escala de Usabilidad del Sistema (SUS). Se utilizó una técnica de entrevista semiestructurada con grabación de audio para permitir la libre expresión de las percepciones de los participantes relacionadas con el IDRA. La información de las entrevistas fue categorizada y analizada por los autores.

Resultados

En la primera revisión, tres artículos analizaban modelos bioinformáticos que integraban algoritmos de IA en protocolos de identificación y cuantificación establecidos, que se utilizan a menudo en las ciencias ómicas. Un total de 13 artículos subrayaron el desarrollo de diferentes algoritmos de IA, por ejemplo, aprendizaje automático, aprendizaje profundo y redes neuronales convolucionales para apoyar la decisión clínica y aumentar los niveles de precisión y exactitud del proceso de rehabilitación. De estos, 6 estudios desarrollaron modelos de IA para el reconocimiento del tipo de implante. La mayoría de los artículos identificados utilizaron algoritmos de IA como herramienta de apoyo clínico, a diferencia de los artículos que aplicaron estrategias bioinformáticas combinando el conocimiento de los algoritmos de IA con la experiencia en Omics. Los criterios convencionales utilizados actualmente como técnica para el diagnóstico y seguimiento de los implantes dentales son insuficientes y presentan una baja precisión. Los modelos que aplican algoritmos de IA combinados con metodologías de precisión y biomarcadores son extremadamente útiles en la creación de la medicina de precisión, permitiendo a los médicos dentistas prever el éxito del implante. Se necesitan herramientas que integren los distintos tipos de datos, incluidos los de imagen, moleculares, factores de riesgo y características del implante, para realizar una predicción más precisa y personalizada del éxito del implante.

En la segunda revisión se descubrió que los kits de prueba PerioSafe® PRO DRS (dentognostics GmbH, Jena) e ImplantSafe® DR (dentognostics GmbH, Jena ORALyzer®), ya utilizados clínicamente, pueden ser una herramienta complementaria útil para mejorar el diagnóstico y el pronóstico de las enfermedades periodontales/periimplantarias. Con los avances de la tecnología de sensores, los biosensores pueden realizar un seguimiento diario de los implantes dentales o las enfermedades periodontales, contribuyendo a la atención sanitaria personal y mejorando el statu quo actual de la gestión sanitaria y la salud humana. Cada vez se da más importancia al papel de los biomarcadores en el diagnóstico y seguimiento de las enfermedades periodontales y periimplantarias. Combinando estas estrategias con los protocolos tradicionales, los profesionales podrían aumentar la precisión de la detección precoz de las enfermedades periodontales y periimplantarias, la predicción de la progresión de la enfermedad y el seguimiento de los resultados del tratamiento.

En cuanto a la prueba de utilidad de la herramienta IDRA, hasta donde sabemos, este fue el primer estudio realizado para desarrollar una prueba de utilidad cualitativa de IDRA, evaluando la eficacia, la eficiencia y la satisfacción de los usuarios. Hubo más variaciones en las respuestas cuanto mayor era el grado de complejidad del caso clínico. En general, los participantes clasificaron la herramienta como buena, obteniendo unos valores de utilidad de 77,2 (DE 19,8) y de aprendizaje de 73,2 (DE 24,5). Para mejorar la herramienta IDRA deberían tenerse en cuenta cuatro factores adicionales 1) considerar la relación entre el ángulo de contorno y la altura del tejido periimplantario; 2) clasificación periodontal automática en la herramienta IDRA tras completar el periodontograma en el software clínico; 3) presentación de un diagrama de flujo que ayude a tomar decisiones terapéuticas junto con la puntuación final definida por la herramienta IDRA; 4) integración de pruebas de precisión como Implantsafe® DR (dentognostics gmbh, Jena) y Oralyzer®(dentognostics gmbh, Jena).

La etiología y la patogenia de las enfermedades periimplantarias son multifactoriales. Estas herramientas deben seguir una integración natural para poder aplicarse fácilmente en un entorno clínico. Es importante estudiar su utilidad desde el punto de vista de los clínicos, evaluando la eficacia, la eficiencia y la satisfacción de los usuarios.

Conclusiones

A partir de estos hallazgos, sería factible crear una herramienta piloto que integre los supuestos de la medicina de precisión, incorporando estrategias actualizadas para apoyar el diagnóstico y predecir el éxito del implante dental. Esta herramienta podría ser vista como una versión actualizada de IDRA, basadas en la literatura.

La herramienta piloto creada se denomina Implant Failure Prediction Tool - IFPT. El IFPT aún no se ha transformado a formato digital, sólo existe como diseño conceptual. Actualmente, esta herramienta reúne todas las condiciones para servir de ayuda en el diagnóstico precoz de las enfermedades periimplantarias, como la mucositis y la periimplantitis, a través de los kits de prueba ImplantSafe®. Su cumplimentación y el cálculo del riesgo siguen la misma lógica de IDRA. Sin embargo, para mejorar la comunicación médico-paciente y facilitar al paciente la comprensión y el seguimiento de su propio caso, el resultado proporcionado por el IFPT se ofrece como señal de tráfico, además de la indicación escrita del riesgo de desarrollar una enfermedad periimplantaria. Así, desde el punto de vista del paciente, cuanto más verdoso es el diagrama, más posibilidades de éxito del implante tiene el paciente. Si aparece un vector amarillo, significa que el paciente debe modular su comportamiento para cambiarlo al nivel verde; cuanto más rojos aparezcan en el diagrama, mayor será el riesgo de desarrollar una enfermedad periimplantaria.

En un futuro previsible, funcionará como una herramienta individualizada que predecirá con exactitud el éxito del implante dental. Actualmente, lo que está a nuestro alcance es empezar a crear un modelo de diagnóstico y pronóstico implantario. Definir una metodología de estudio longitudinal que permita cargar en el IFPT el mayor número posible de casos clínicos ("inputs") y, a través del seguimiento de estos pacientes, identificar/diagnosticar posibles hallazgos de periimplantitis, mucositis o salud periimplantaria ("outcomes") a lo largo del tiempo. De esta forma, a medida que se procesan los datos mediante algoritmos de AI, se pueden identificar las variables/predictores con mayor significación para la determinación del fracaso del implante y, al mismo tiempo, sus respectivos pesos en el algoritmo predictivo. Esta metodología se detallará a lo largo del siguiente tema de discusión. Esta herramienta utilizará algoritmos de IA, concretamente tecnología de redes neuronales artificiales, lo que permitirá que la herramienta acumule diferentes funciones a medida que se utilice. Las redes neuronales artificiales son modelos muy flexibles y se han utilizado en medicina para explorar las relaciones entre diversas variables fisiológicas y construir modelos predictivos. De este modo es posible definir un algoritmo capaz de indicar con exactitud y precisión la respuesta al tratamiento.

1 INTRODUCTION

One of the most challenging goals in the field of oral rehabilitation is the treatment of partial and complete edentulous patients in terms of function and esthetics. Despite the reason that may have caused the loss of teeth, dental or implant-supported oral rehabilitation should always be planned based on its predictability and lifetime.

1.1 IMPLANT-SUPPORTED ORAL REHABILITATION

Considering the growth of population and the average lifespan, there are currently much more people looking for treatments and solutions for the teeth they had lost, which ultimately resulted in a higher demand for bone regeneration treatments, as well as dental implants (1–4).

Despite the many recent advances in implantology, the success of implant-supported oral rehabilitation remains a challenge. Implant failure can result from various factors, such as Peri-implantitis, inadequate osseointegration, surgical technique, systemic conditions, and patient selection (5,6).

A major, if not the major, risk factor for implant failure is the emergence of peri-implant diseases. These diseases have been the subject of several consensus conferences, the most recent in 2017 (7), being classified as peri-implant mucositis, in which the inflammation is confined to the soft tissues (3), or peri-implantitis, in which the inflammatory process also extends to the supporting bone, with progressive loss beyond biological bone remodeling (7). It is generally agreed that both, peri-implant mucositis and peri-implantitis, have an infectious etiology and that peri-implant mucositis usually precedes peri-implantitis (7). However, the conversion from mucositis to peri-implantitis remains an enigma, as peri-implantitis occurs primarily as a result of an overwhelming bacterial insult and subsequent host immune response (3). The presence of pathogens is necessary but not sufficient for the development of peri-implantitis, since it is the osteo-immunoinflammatory mediators produced by the host response that exert an essential impact on the breakdown of peri-implant tissue.

One of the most feared dental complications is peri-implantitis, which involves a loss of peri-implant bone tissue due to bacterial invasion of peri-implant tissues as a result of an imbalance between bacterial quantity/quality and the host's defensive capabilities (4). Peri-implant tissues have a lower capacity for soft tissue sealing (epithelial and connective) than the original tooth (8). This protective band of connective tissue and epithelium is known as the biological space, with dimensions ranging from 1.2 to 2.0 mm in height for epithelial tissue and 1.0 to 1.5 mm in height for connective tissue (9). These dimensions correlate to the degree of bone remodeling that occurs after the connection of the abutment (10,11). The effect of various morphological characteristics, surface treatments and manufacturing materials on early peri-implant bone loss has been studied with the aim of promoting a good epithelial-connective seal which will protect the peri-implant marginal bone (12,13). The development of tools that integrate the risk factors associated with failure is crucial for enhancing implant success rates. These tools enable clinicians to assess the risk of failure, make informed decisions, customize treatment plans, and implement preventive measures. Ultimately, they contribute to improving the overall success and long-term outcomes of oral rehabilitation with implants.

1.2 BIOCOMPATIBILITY

The characteristics of the synthetic substances used for substitution or increase of biological tissues have always been the object of great interest in dental medicine. A biomaterial is a natural or man-made substance for direct use, as supplement or substitute for functions in tissues. Biomaterials can include cells, tissues or devices developed for implantation (14).

The evolution of the definition of biocompatibility can be described as follows shape: in the 1970s biocompatibility was defined in terms of damage minimum for the recipient or the biomaterial, that is, the material that created the least damage to the adjacent tissues would be the most biocompatible; in the 1980s it shifted to an approach regarding the stable interaction for the active substrates, which were intended to positively influence the response of tissues. In the last decade of the 20th century, the biocompatibility studies of the materials focused on the materials chemically and mechanically active, associated with growth substances and morphogenic (15,16). Biomaterials are currently being studied in the sense of that its modified surface can directly influence the response of tissues adjacent in the short or medium term (16). Biocompatibility of any human tissue substitute is a requirement fundamental to all substances and materials used in medicine, so we can classify different materials as biocompatible or bioincompatible. If we refer to dental implants or bone regeneration materials, we can classify biocompatible materials as biotolerable, bioinert, or bioactive (17). A material is designated biotolerable when it is separated from bone by a layer of tissue fibrous and the substances it releases do not cause local or systemic toxic reactions. In a bioinert material there is a contact osteogenesis, with the formation of bone around the implant, without soft tissue interposition. And finally, a material bioactive allows an effective connection between the reactive surface of the implant and the bone close to the implant or implanted material. This connection is characterized by the presence of a calcified amorphous substance that supports high forces (17). Bioabsorbable, bioactive and biologically stable materials, including a great variety of synthetic or natural polymers, ceramics, glasses and composites, come being studied in the regeneration of alveolar bone and in the development of implants three-dimensional structures used in different surgical applications (18).

1.3 OSSEOINTEGRATION

In 1983, Brånemark defined the osseointegration as “the firm, direct and stable union between the vital bone and the implant, without the interposition of another type of tissue between them” (19).

This process consists of the formation of a stable and mature bone matrix, creating a strong relationship between bone and implant. In 1986, the American Academy of Implant Dentistry defined osseointegration as “the contact that is established no non-osseous tissue interface between normal remodeled bone and an implant, which results in a sustained transfer and distribution of the load from the implant to the within the bone tissue”(20). The process that occurs in the osseointegration of a dental implant is like that primary bone healing process. Initially, there is blood present between the implant and bone to later form a blood clot. that same clot is subsequently transformed by cells of the immune system such as phagocytes, polymorphonuclear leukocytes, lymphoid cells, and macrophages. The activity level of phagocytes reaches its maximum during the time elapsed from the first to the third day after implant placement surgery. During this period the formation of the callus takes place, which contains fibroblasts, fibrous tissue and phagocytes (21). The callus becomes dense connective tissue, and the mesenchymal cells differentiate into osteoblasts and fibroblasts. Bone cells attach to the surface of the implant by chemical and mechanical methods (21).

1.4 PRIMARY STABILITY

The primary stability of the implant is a fundamental requirement to achieve its osseointegration. Primary implant stability is defined as the biomechanical stability upon implant insertion, being influenced by numerous factors, such as: bone quantity and quality, the geometric design of the implant, surgical technique, and insertion torque. From this stability, new bone develops around the surface of the implant, constituting a biological fixation named secondary implant stability (22,23). Torque forces are usually considered ≥30Ncm are those necessary to produce adequate primary stability so that the osseointegration process occurs, even though forces ≥50Ncm reduce the micro movements and appear not to induce alveolar bone damage. These higher forces are especially important when applied in cases of implant insertions in alveolar ridges or post-extraction alveoli rehabilitated with immediate prostheses. The absence of micro movements is a fundamental requirement for a process of predictable osseointegration, even more so when we talk about this type of case (24). The concept of primary stability is also related to the macroscopic design of the implant used. The format cylindrical or conical can cause different insertion torques leading to different clinical actions by the surgeon at the time of implant placement. According to the authors, the data obtained in their in vitro study indicate that the design of the implant requires specific insertion torque forces to obtain stability ideal primary (10,24,25).

1.5 PERI-IMPLANT FAILURE

Endosseous dental implants have been a successful treatment alternative for restoring missing teeth. However, treatment with dental implants still fails, evidenced by reports reviewing reasons for implant failure (25–27). Implant Failure is defined as failure of an implant to fulfil its purpose (functional or esthetic) because of mechanical or biological reasons, within a range that has been differentiated from “failure” to “complication”(28,29). Initially, the term complication was used in literature for reversible conditions, that is, those conditions which could be corrected. In recent literature, however, the term failure has been used for both reversible as well as irreversible conditions associated with dental implants (29). Esposito *et al*.(30) stated that the reasons for failure of dental implants include biological failures (related to biological processes such as inadequacy in maintaining osseointegration) and mechanical failures (including fractures of implants, coatings, connecting screws, and prostheses). A study published in 1999 divided dental implant failures into 7 classes: 1) according to etiology (host factor, surgical failure, implant selection and restorative failure), 2) timing of the failure, 3) condition of failure, 4) responsible personnel, 5) mode of failure, 6) tissues involved and the 7) origin (30). Implant failures have also been classified into four main categories as per Chee W. *et al*.(25)- 1) loss of integration, 2) positional failures 3) soft tissue defects, and 4) biomechanical failures. Goodacre *et al*.(26) divided implant complications into 6 categories: 1) surgical, 2) implant loss, 3) bone loss, 4) peri-implant soft tissue, 5) mechanical, and 6) esthetic/phonetic. The authors stated that fourteen mechanical complications have been identified in literature and their incidence ranged from 30% (loss of retention of implant overdenture clip/ attachment) to 1% (implant fractures) risk of mechanical complications and failures play a major role in implant dentistry because they can lead to increased repair and remake, waste of time, financial resources, and adversely affect the patient's quality of life (25,27). Early detection of implant failure is important as "a failing implant can be saved if it is detected early, whereas a failed implant cannot be saved and must be removed" (30,31).

1.6 DENTAL IMPLANTS FOLLOW-UP

The maintenance phase in implantology is key to the success of the treatment and should be an objective in the planning of the cases to obtain optimal conditions that promote hygienic measures by the patient and the professional.

According to Benakatti *et al* (32) 'dental implants will need maintenance as long as they remain in the patient's oral cavity'(32). Therefore, it is necessary to carry out control appointments to prevent or treat these complications. For this, several information/data about the rehabilitation are needed, namely the implant system used, fixation method and abutment used. Normally, patient history and radiographic examination are tools that allow the clinician to identify the implant system. However, the patient's history is not always accessible, and the identification of the implant system through radiographic examination requires a lot of effort and experience from the professional, once the process involves processing a large amount of information such as implant features such as shape, size, threads, connection, apex and collar (33,34).

Due to the complexity resulting from the multifactorial nature of implant-supported rehabilitation, the development of methodologies able to integrate all the factors/predictors is only possible with the use of informatic tools. In recent years, some approaches have already been made in this direction whereby artificial intelligence (AI) algorithms can support the diagnosis or identify dental implants through radiographic images. These strategies support the prognosis of the implant, predicting eventual clinical conditions such as early bone loss, mucositis or peri-implantitis (35,36). In addition, when using methods based on advanced neural networks – machine learning – it is possible to foresee how complex it might be and the potential risk involved during the process of the dental implants rehabilitation (37,38).

All the scientific evidence, as well as the assessment tools used nowadays by professionals are strictly based on clinical, analytical, and radiographic parameters which, indeed, will provide the doctor with some limited therapeutic guidelines to deal with the multi-factorial complexity of the implant-supported rehabilitation procedures. Furthermore, from the point of view of diagnosing and staging peri-implant diseases, there are methods that can only register the pre-existent state and not the current condition itself, not considering the patient's clinical picture. Moreover, it does not contemplate systemic conditions, lifestyle, hormonal changes, and ageing, among other aspects, related to individual inflammatory processes which may consequently influence the local immunological response, either around a tooth area (periodontitis), or around a dental implant area (peri-implantitis).

Currently, the role of pathogens and their influence on periodontal/peri-implant diseases are well known (39,40). Nevertheless, it is established that oral dysbiotic *status* are necessary to trigger these same pathologies. This understanding allowed the identification and confirmation of several individual conditions as risk factors with immunological impact. Ultimately, the "immunophenotype" plays a key-role in the process of developing oral inflammatory conditions, because there are people with a hyper reactive genetic predisposition, who intensely react, when exposed to small amounts of bacterial biofilm (41).

By considering all these facts and recognizing the multifactorial complexity of oral inflammatory disease, the necessity to provide accurate analyses based on a standard clinical protocol requires diagnoses supported by *Omic* technologies, such as proteomic. *Omics* aims at the collective characterization and quantification of biological molecules that translate into the structure, dynamics and function of an organism. *Omics* technologies have emerged as a powerful tool to investigate different molecular mechanisms between health and disease states, discovering molecules (Biomarkers) commonly used in medicine to objectively determine the state of the disease or responses to a therapeutic intervention and that can be the targets of new therapies (41,42).

This methodology is the key for the introduction of precision medicine into dentistry, mainly in the field of oral rehabilitation, because it can adapt the procedure to follow, considering the patient's biological, social (economic and educational) and lifestyle characteristics. Despite this, it can prudently work against pathologies that might take place and their progression in early stages. To give a credible diagnosis and a specific treatment plan, respecting every single patient's needs, multiples research in many different health fields have appeared, by focusing on genomics, proteomics and metabolomics. The concept of precision medicine does not necessarily mean the creation of medical devices exclusively for one patient, but the ability to classify individual members into subpopulations that differ in their susceptibility to a specific disease or treatment. The major goal is to reduce diagnosis mistakes, to develop results and to avoid unnecessary collateral effects, by clarifying the reason why such individual can develop a peri-implantitis clinical picture, when compared to others with same conditions that did not develop the same state (41,43).

1.7 IMPROVING THE SUCCESS OF IMPLANT-SUPPORTED ORAL REHABILITATION - PRECISION MEDICINE APPROACH

Precision Medicine (PM) can be described as a developing area, in which diagnosis is based on the identification of biological markers, often genetic, that assist the health professional in deciding which treatment or protocol will work best for each patient. This is not intended to create a specific treatment for an individual, but rather to group users into subpopulations according to their susceptibility to a disease and/or a specific treatment, with the goal of reducing diagnostic errors and avoiding side effects in treatment. Thus, it can be said that PM consists in a process of collection and selection of individual data with the goal of joining them to a group of people that present similar characteristics associated with a particular condition. PM depends on "High-throughput" technologies for large-scale production of biological data, as well as advances in computer technologies and the changing paradigm of health care delivery (44). The starting point of this process is the in-depth phenotyping of individuals which, as shown in figure 1, consists of collecting individual patient data at different levels, from the simplest to the most complex data; the more complex the data obtained, the more likely it is to reach the PM assumption. These data range from medical history, lifestyle, physical examination, basic laboratory tests, radiographic imaging, functional diagnostics, immunology, and histology to data obtained from the omics sciences (45). Once obtained, data processing is divided into three stages, firstly they are pre-processed, including the selection of variables. In a second step, the variables selected in the previous step can be used to develop and validate diagnostic and prognostic models, and the clinical relevance of these models can be gauged through studies that demonstrate the effect of their implementation. Finally, specific models that aim to predict treatment response are developed and validated, based on the models developed in the previous steps. The results obtained between steps 1 and 3 are used for the deep phenotyping stage to define the evaluation of patients. In order to make the use of the developed algorithms accessible and user-friendly in a clinical setting, the models obtained from steps 2 and 3 should be shared and communicated (45). The shading indicates that the more voluminous and complex the dataset becomes, the more likely it is to meet the presupposition for precision medicine and big data. Data are then forwarded for further analysis to tracks 1–3.

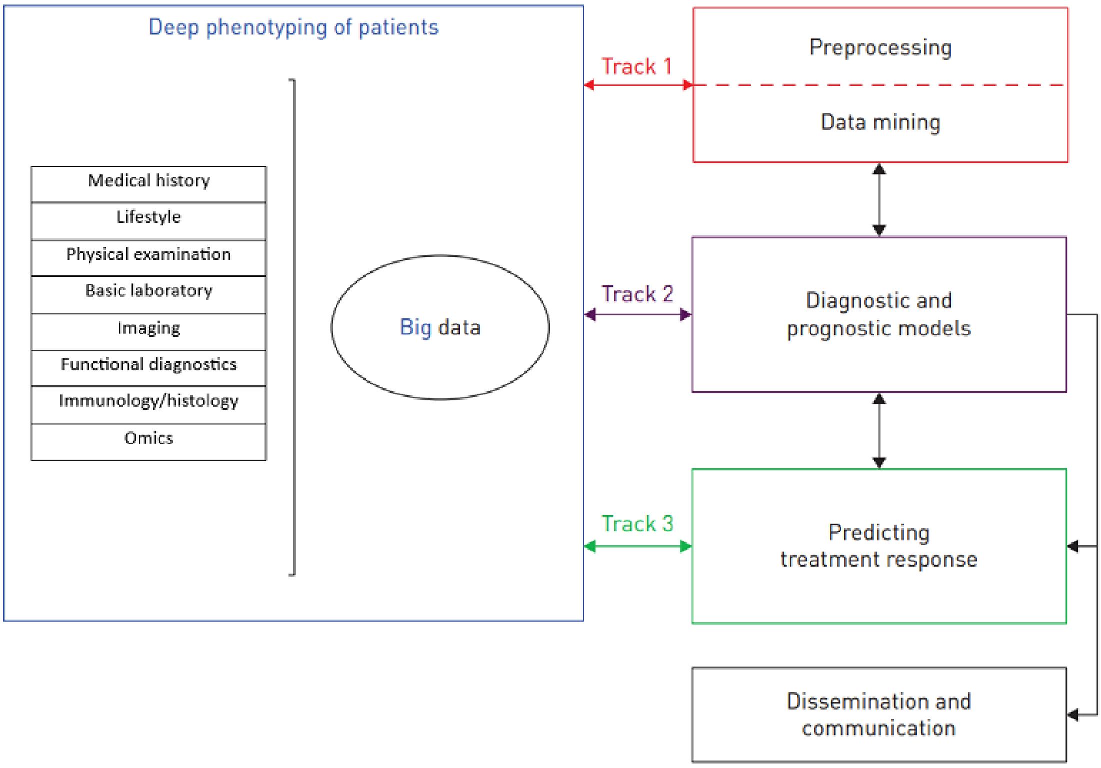

Figure 1: The process of deep phenotyping in precision medicine (adapted from König et al. (45)).

1.7.1 The need to adapt concepts

Up to now, patient classification has aimed at placing an individual within a group, whose members have similar characteristics regarding the pathology in question, for example clinical signs and symptoms. However, a change in the current paradigm is needed and the aim should be to place each subject in an exclusive, homogeneous and unbiased group representing a particular phenotype of interest, in which the members of the group have a similar degree of risk of developing a particular condition, as well as the progression and response to treatment of the condition (46).

Thus, Precision dental medicine (PDM) emerges, which, like Precision Medicine, has as its goal the deep phenotyping of as many individuals as possible, in other words, it uses the data collected from the patient, to insert him/her in a group of individuals that present similar characteristics associated to a specific condition. Therefore, the need arises to find specific biomarkers for a given condition, and at this moment it is possible to identify in literature several efforts towards the determination of new biological markers associated to oral diseases, especially Periodontitis and Dental Caries. In this sense, microbiology has been playing a fundamental role in these advances, since it allows the detection and quantification of several microorganisms associated to different pathologies, thus allowing their prediction, diagnosis, and revealing new therapeutic targets.

By themselves, the forms of providing oral care already have very personal characteristics. Since clinicians themselves have come to recognize different variations between patients associated with the same oral pathologies, there has been an adaptation of oral health care on an individual basis based on clinical history and environmental and behavioral factors (47). Since most oral diseases result from a complex interaction between genetic, biological, behavioral and environmental factors, there was a need to understand in more detail the processes that lead to the disease state, thus enabling the use of new approaches to assess risks, improving disease prevention and guiding treatment. These new methodologies are already being put into clinical practice in medicine and can be adapted to different areas of health, including dentistry (47,48).

1.7.2 Factors to consider for the application of Precision Dental Medicine

To develop a true Precision Dentistry, several factors must be considered that allow for the phenotypic characterization of individuals, of which we highlight those presented below.

1.7.2.1 Medical history in Dentistry

In dental medicine, diagnosis depends on several factors, including intra and extra-oral examination, complementary diagnostic tests, as we will discuss in greater detail later, and the patient's own medical history.

The medical history may include information such as comorbidities, current medication, general medical and dental history, family history, among others, which makes it very important both for diagnosis purposes and for predicting the prevalence of oral diseases. However, not infrequently, the filling in of this type of information is wrongly devalued and discarded both by the health professionals themselves and by the patients themselves, who end up omitting information that may be important in the treatment decision (49).

Also, for the implementation of precision dental medicine, there is a need to have at the researchers' disposal a large set of data so the neglect of this stage of diagnosis can often be a challenge for the creation of new methods of prediction, diagnosis and treatment.

1.7.2.2 Complementary diagnostic examinations

The clinical practice of dentistry depends to a great extent on the ability to make a diagnosis. For this to be possible, it is necessary to use various exams that will support the clinical decision. In general, the most used are intra-oral clinical observation and the use of imaging. However, in less common cases, microscopy and biochemical tests are also used, especially in the area of Oral Medicine to check for the presence of alterations in the oral tissues that are characteristic of certain oral pathologies (50).

1.7.2.3 Imaging exams

Imaging exams include all data resulting from several techniques to obtain images of the human body, such as radiographs, images resulting from intraoral scanners, among others, thus representing one of the most used means of diagnosis in the oral health area. The analysis of this type of register is complex and susceptible to human error due to interpretation biases. For this reason, AI strategies have been increasingly developed to make this process more efficient. Artificial Intelligence corresponds to the part of computer science whose occupation is to design a system with characteristics that can be associated with human intelligence, for example, learning, reasoning, language understanding, among others. Within it, there are some subcategories such as Machine Learning. This is the area responsible for improving automated learning capacity, without human influence.

As a subgroup of Machine Learning, there is a very popular area called Deep Learning which is dedicated to the processing of data and its metadata (51). The difference between these two areas is associated with the way each algorithm learns. In systems that use Deep Learning the extraction of data is automated, eliminating human intervention, allowing even larger data sets. On the other hand, systems that use Machine Learning are more dependent on human intervention for learning processes. Deep Learning also presents subgroups, as is the case of Neural Networks, whose objective is the use of several algorithms to identify relations in a set of several distinct data through a process similar to what occurs in the human brain, justifying the analogy of these systems to the human neuron system (52).

1.7.2.4 Complementary diagnostic tests supported by biological data

Some of the complementary diagnostic tests with potential application in PDM are based on biological data which may be used as biomarkers. Among these we can highlight several biomolecules, microorganisms and even several ions, all of which can be found in saliva, which thus assumes an essential role in the development of PDM.

Since saliva is a biofluid that is present in large quantities in the oral cavity and has characteristics very similar to the oral space, such as microbiome and proteome, there is great interest in its analysis for diagnostic purposes. This fluid is secreted by three pairs of major salivary glands, namely the parotid, submandibular and sublingual, and from several smaller glands that are secreting saliva continuously directly into the oral cavity, making saliva the most available biological fluid in the human body (53).

This consists mostly of water, representing 99% of all its constitution. Furthermore, a complex mixture that includes urea, ammonia, acid, glucose, cholesterol, fatty acids, triglycerides, neutral lipids, glycolipids, amino acids, steroid hormones, glycoproteins, among others, is part of it. In addition, it also has high concentrations of Na^{+}, Cl^{-}, Ca^{2+}, K^{+}, HCO_3^{-}, $H_2PO_4^{-}$, F^{-}, I^{-} e Mg^{2+} (54).

In its composition, similarly to the oral space, more than 1000 microorganisms related to oral and systemic diseases can be identified. Due to its rich composition, both at microbiome and proteome level where over 4000 human proteins and about 15000 microbial proteins with biological activity can be identified, saliva is currently considered a pool of biomarkers, ranging from biochemical changes of proteins, DNA and RNA to the very structure of the microbiome (55–58).

Its collection, due to its characteristics, can be performed in a simple, safe and non-invasive way, so it shows great potential as a diagnostic fluid. However, several factors may alter its composition, as well as its total amount, including: time of day, hydration, smoking, taking medication that causes xerostomia and also factors related to systemic conditions (53,56,59).

Considering its composition and characteristics, interest in saliva as a diagnostic biofluid has been growing over the years. Thus, in 2008 the concept of "salivaomics" emerged, which includes the different areas of the omics sciences, which we will cover in more detail, which can be used for the analysis of saliva samples. About 70% of the genome found in saliva is human with the remaining 30% associated with the oral microbiome and, although the amount of DNA available in saliva is approximately 10 times less than that available in blood, it is still sufficient for genotyping techniques to work effectively, such as polymerase chain reaction (PCR), making it a viable alternative to blood tests (60–62). Its transcriptomic analysis, in turn, can also provide important information regarding the stages of disease because, although the genome is the same in all cells, they show distinct RNA composition patterns, and the polymerase chain reaction with reverse transcriptase and microarray techniques are the most frequently used analyses. Since the comprehensive analysis of the salivary proteome is fundamental to assess its full potential in terms of diagnosis, the field of proteomics can also be used in its analysis and the most used techniques are nuclear magnetic resonance spectroscopy (NMR) together with mass spectrometry. Finally, the study of its metabolites such as nucleic acids, vitamins, lipids, organic acids, carbohydrates, thiols and amino acids can provide insight regarding the general health status or its modification during systemic diseases (62–64).

Similarly, in 2012 the term Oraloma was first suggested as the set of all molecules present in the oral cavity of human and microbial origin (57). These molecules were then brought together in a database called OralCard. OralCard is a Web Application that allows mining over an integrative database containing manually curated information about the oral cavity proteome with the addition of the experimentally determined oral proteome of microbial origin. OralCard promptly allows a wide range of data associations, for instance, whether a protein is involved in any specific pathological condition, which microbial proteins may be present in the oral cavity, or what the annotated functions of any given protein are and in which pathways it is implicated. Furthermore, for each protein it is possible to explore the structural and functional details. OralCard facilitates the interpretation of proteomic data of the oral cavity and will therefore be a valuable resource for researchers aiming to understand the physiologies of oral cavity in health and disease and probing for potential biomarkers for oral and systemic diseases (65).

A key objective of the OralCard project was to collect information on proteins present in the oral cavity and integrate that information, providing associations between proteins, diseases, pathways, gene ontologies and organisms. To achieve this goal, SalivaTec team carried out a first survey of online. The OralCard interface was developed to automatically retrieve and update the Oralome database with the collected information and present it in a user-friendly way. This is extremely useful as it joins in one single endpoint relevant proteomic data concerning oral proteins, which increases the time–

efficiency ratio when searching for a protein, disease or microorganism and allows for systematic approaches in exploration of the oral proteome.

This database later evolved into SalivaTecDB (salivatec.viseu.ucp.pt), a web-based database providing information on salivary biomarkers found in humans. In SalivaDB, data can be browsed by (i) Biomarker Category—this module allows the user to choose the category of biomarkers which includes gene, protein, miRNA, metabolite and microbe; (ii) Biomarker Type—this module contains three options encompassing diagnostic, prognostic and both types of biomarkers; (iii) Disease Category—this allows user to select biomarkers from a wide range of disorders affecting humans; and (iv) Exosomal Origin—this module helps the user to choose the biomarkers that were derived from the extracellular vesicles—exosomes. These browse options result in a list of experimentally validated salivary biomarkers with expansive information, including their PMIDs, experiment details and more. In SalivaDB, basic and advanced search modules have been incorporated to make searching easier. The user can search for biomarkers by Biomarker Name, Biomarker Category, Biomarker Type, Disease Category, Disease Name, Type of Cancer and Exosomal Origin. In the basic search module, the output can be adjusted based on the search query. The advanced search feature allows users to simultaneously enter numerous queries using Boolean expressions (e.g. AND, NOT and OR)(66).

Recently, through the implementation of PDM several biomolecules such as enzymes, interleukins and growth factors, as well as toxic substances can be measured in samples collected from the oral cavity. Thus, as mentioned above, saliva has been constantly growing as a diagnostic tool, since by counting or detecting altered concentrations or the less usual presence of certain biomolecules makes it possible for them to be used as biomarkers for both diagnosis and prognosis of various oral diseases (50,67).

A biomarker can be defined as a biological characteristic that can be objectively measured and assessed as a normal biological indicator, of pathogenic processes or response to a particular therapeutic intervention. In the year 2000, Perera and Weinstein (68) suggested a classification of biomarkers based on the events occurring from exposure to the disease state, as shown in figure 2. In this figure we can observe the different relations of biomarkers with the different stages from a state of health to the contraction of a certain condition, which may serve to understand its etiology, pathogenesis and detection, identifying risk factors, its induction, latency and diagnosis, also allowing the understanding of the disease state itself, which in turn makes its monitoring viable, as well as the prediction of its prognosis. This figure also aims to demonstrate the relationships of biomarkers with the different stages from a state of health to the contraction of a certain condition, demonstrating their utilities throughout these processes, such as determination of risk factors, monitoring, prognosis, among others (68,69).

In summary, biomarkers have various uses, such as, for example, in the characterization of diseases, which can also help in their diagnosis and monitoring, and in their division into different stages. They can also be used to obtain information about prognosis, response to treatment and to predict adverse responses to certain drugs (70).

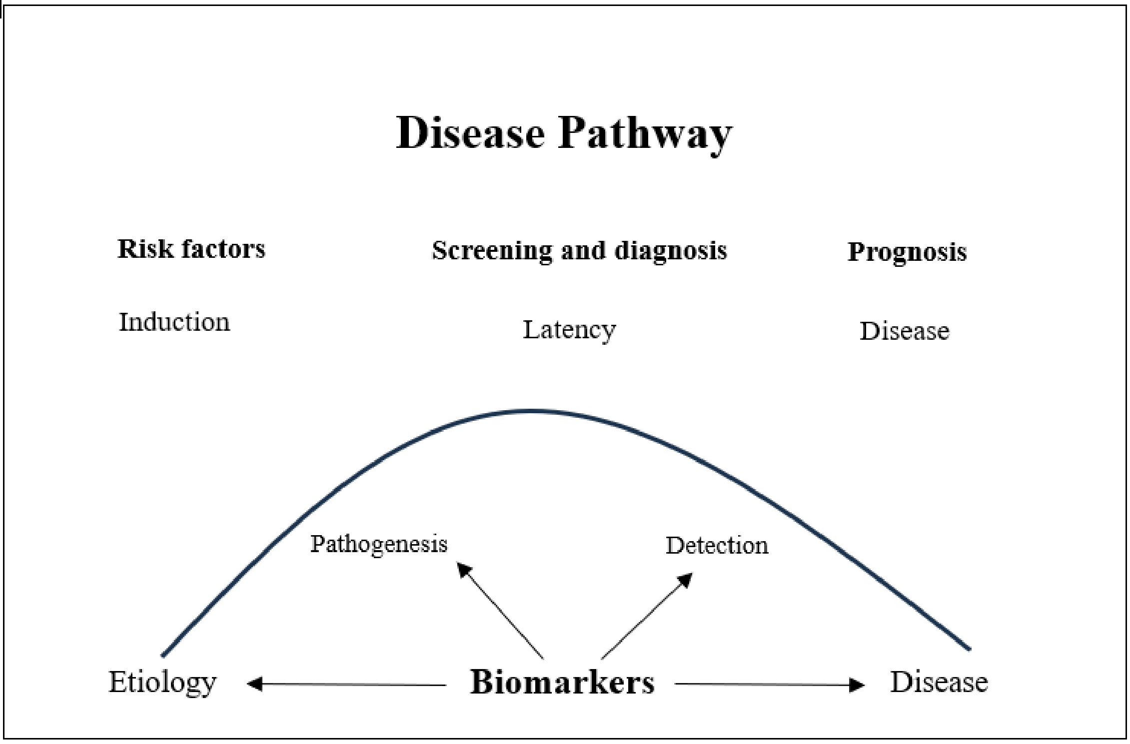

Figure 2: Disease pathways and importance of biomarkers (adapted from Mayeux R. 2004 [61]).

As mentioned above, PM and PDM rely heavily on the collection, processing and analysis of individual patient data, through which it is possible to associate new biomarkers to various oral diseases. Currently, due to the technological development in recent years, the determination of biomarkers is increasingly within our reach. The Optical Sciences are examples of these advances. These are composed of 4 distinct areas, which are Genomics, Transcriptomics, Proteomics and Metabolomics.

Recent advances in omics technologies have led to efforts to characterize the molecular changes underlying the development and progression of a wide variety of human diseases. Thus, multi-omic analyses, which encompass the above-mentioned omics areas, have been proposed as the key to advancing precision medicine in the clinic.

Genomics is the field responsible for analyzing the human genome, in other words, the complete set of an organism's DNA, this genetic material being predominantly found in the nuclei of human cells. In recent years the study of the genome has been carried out using techniques such as Genome-Wide Association Studies (GWAS), among others, which have provided many variations in the DNA sequence associated with different diseases and characteristics in humans. Figure 3 shows a timeline starting in 1900 that is divided in two, with the left side corresponding to research associated with the genome and the right side to different specific milestones achieved in dentistry through genome analysis (46,71,72).

Some interesting discoveries associated with dentistry are the identification in 1980 of the relationship between the AMELX gene and the prevalence of Amelogenesis Imperfecta, which demonstrates several advantages as a genetic biomarker for predicting this pathology and, through further research, new therapeutic targets can be determined, thereby revolutionizing the approach to this type of pathology (73). In addition, more recently in 2020 there are reports of new intrauterine therapies in patients with ectodermal dysplasia. Oligodontia the subject has 6 or more missing teeth, which is very frequently occur in patients with this pathology. Up to now, the rehabilitation of these patients was carried out through the use of dental prostheses or dental implants, however, currently, some studies report the intrauterine substitution of proteins associated with dental formation that present positive results associated with the appearance of new dental germs, improving the prognosis of these patients and reducing the need for rehabilitation (71).

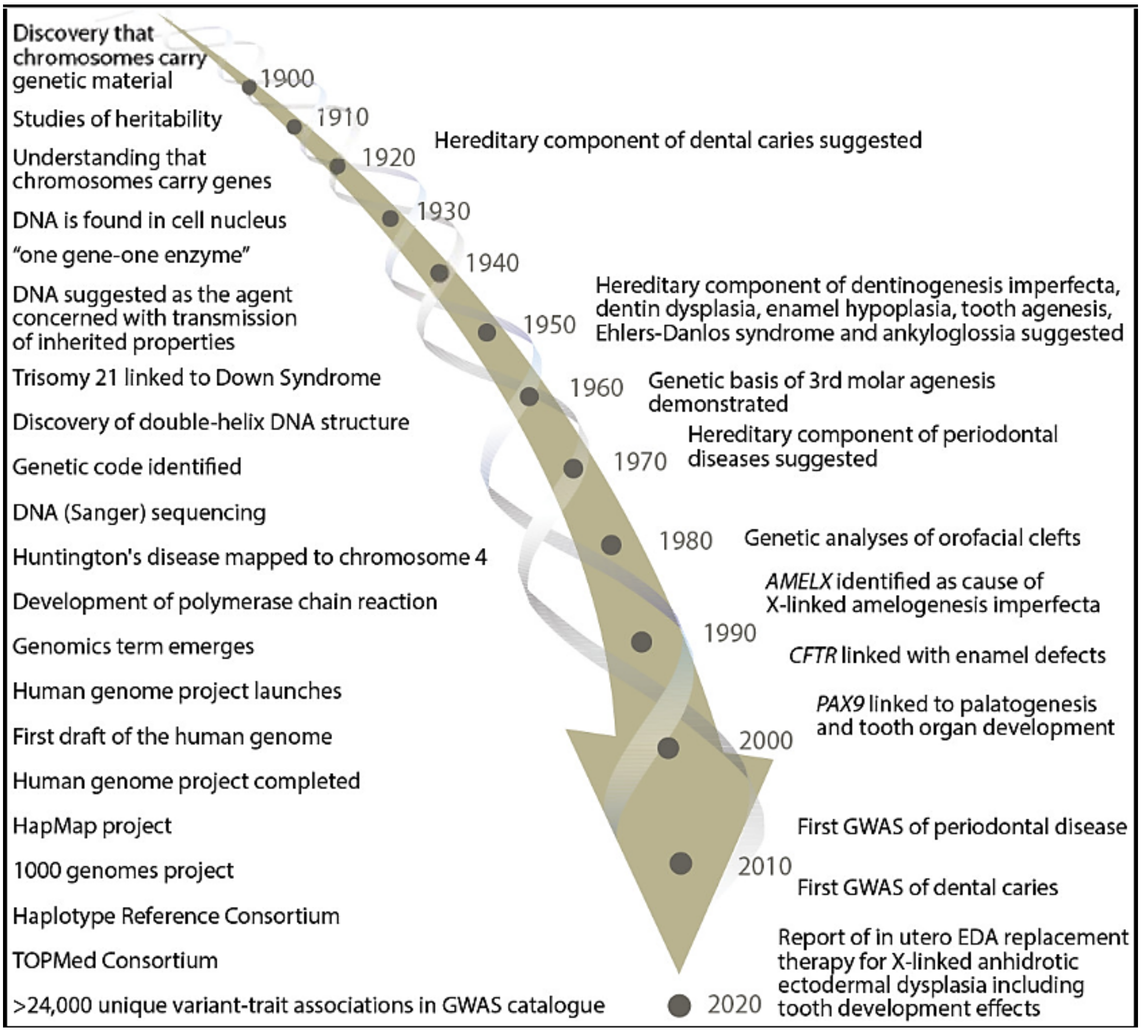

Figure 3: Timeline of genome research (left side) and oral health–specific landmark evolvements and illustrative reports (right side) since 1900(71).

With the evolution of sequencing techniques, genetic research has resorted to this approach to analyze the transcriptome of cells and determine how alterations during the transcription process can be used for diagnostic purposes and to identify molecular mechanisms associated with the development and progression of diseases. Thus, the Transcriptomics area is responsible for studying the human transcriptome that includes ribosomal RNA (rRNA), messenger RNA (mRNA), transporter RNA (tRNA), microRNA (miRNA), among others, and its quantitative analysis can be performed through microarrays or RNA sequencing (72,74). Proteomics, in turn, corresponds to the analysis of the proteome, in other words, of all the proteins expressed by a biological system, and the most used techniques in this area are mass spectrometry and electrophoresis. Mass spectrometry is a technique whose objective is the detection and identification of certain molecules by measuring their mass, as well as the characterization of their chemical structure. Firstly, organic compounds are ionized, separating them according to their mass/charge ratio, which allows their qualitative and quantitative detection (72,74). Gel electrophoresis is a technique that aims to separate molecules, such as proteins, DNA and RNA. It involves the migration of particles in a gel as a result of the application of an electric field. In both techniques, the molecules are separated according to their size, which in turn allows them to be used as biomarkers facilitating the diagnosis and monitoring of various pathologies (72,74). There are two major types of biomarkers: biomarkers of exposure, which are used in risk prediction, and biomarkers of disease, which are used in screening and diagnosis and monitoring of disease progression. Biomarkers used in risk prediction, in screening, and as diagnostic tests are well established, and they offer distinct and obvious advantages:

Delineation of events between exposure and disease; Establishment of dose-response; identifications of early events in natural history; identification of mechanisms by which exposure and disease are related; reduction in misclassification of exposures or risk factors and disease; establishment of variability and effect modification; enhanced individual and group risk assessments (75). The classification of many neurological diseases is based on either standardized clinical criteria or histological diagnoses. Biomarkers also have the potential to identify neurological disease at an early stage, to provide a method for homogeneous classification of a disease, and to extend our knowledgebase concerning the underlying disease pathogenesis. These advantages have direct application to all types of clinical investigation, from clinical trials to observational studies in epidemiology.

Finally, the metabolome is the set of metabolites present in each system. Often, metabolites are seen as products resulting from cellular processes, mediated by proteins, so it is assumed that when changes occur these may be the consequence of alterations in the functions of enzymes or proteins. Thus, metabolomics is the area based on the biochemical characterization of metabolites and their variations associated to internal factors, that is, genetic and external, environmental factors (72,74). Mass spectrometry, together with nuclear magnetic resonance are the main techniques used in this area (46,72,74). The oral cavity is an extremely complex environment, considered as the "mirror of the body's health" (56). Interactions occur between tissues and microorganisms, air and food, and it is therefore considered an ideal place to study the relationships between the microbiome and the host, whether they are symbiosis, associated with a state of oral health, or dysbiosis, associated with a state of oral pathology. Therefore, through this monitoring, several parameters can be studied, such as the diversity of the oral microbiome and the biochemical characteristics associated to the biological response of the host. When these parameters are associated to a specific pathology, they can be used as biomarkers, allowing both a more accurate diagnosis and a more specific treatment (43,46,76). As mentioned above, the oral cavity has unique characteristics when compared to other anatomical areas. It has a vast proteome and also a personalized microbiome considered to be the most diverse in the human body. Besides its vast variety, it plays a fundamental role in maintaining the oral health condition, that is, when there is a balance in the microbiome, a favorable oral health condition is expected, however, when there is an imbalance in the oral microbiome (dysbiosis condition), it allows the manifestation of pathogens, causing diseases such as caries, periodontitis, among others. Thus, it is said that the oral cavity is the ideal place to study the relations between the microbiome and the host, since besides its vast taxonomic diversity, it has characteristics that make it easily accessible, allowing the collection of samples through non-invasive techniques, whether through crevicular fluid, dental plaque or, as we will discuss later, saliva.

Taking into account the characteristics of the oral cavity, omics can be considered as a key factor for the implementation of precision dental medicine, as by monitoring the states of balance and imbalance, new biological markers can be found that can be associated to a specific disease, and can also provide new therapeutic targets (77).

Therefore, the importance of biomarkers as a methodology to be implemented in dentistry is recognized, especially in areas where interindividual variability presents a great relevance, such as during biological mechanisms associated to osseointegration and in dental implants late failure processes (mucositis or peri-implantitis).

Considering the aim and transversality of precision medicine, it is imperative to create protocols that aim to respond to its assumptions, ideally through the application of AI algorithms and omics methodologies such as biomarkers. This doctoral thesis aims to take the first steps towards the creation of a protocol to be followed in cases of implant-supported oral rehabilitation, which complies with the assumptions of precision medicine.

2 OBJECTIVES AND JUSTIFICATION

Precision medicine is a relatively new and innovative approach that is beginning to be implemented in dentistry, having been taken an important step forward by the implementation of biomarkers in the new classification of periodontology and peri-implant conditions.

Several fields of dentistry can take advantage of this methodology, however the one that stands out the most is implant-supported oral rehabilitation due to the multifactorial etiology of implant failure, such as osseointegration failure, mucositis or peri-implantitis. Currently, numerous factors associated with these clinical conditions are known, as well as the protocols used in the diagnosis and treatment of these pathologies. However, this methodology is only able to identify the pathology when it is already installed, and not before there is tissue damage. It is necessary to introduce bioinformatic strategies, combining artificial intelligence and *omic* sciences, into conventional clinical protocols widely used and known by dentists, increasing the accuracy of early detection of peri-implant and periodontal diseases, the prediction of disease progression and monitoring of treatment effects.

The specific aims of this study were:

1. To review the literature on bioinformatics (artificial intelligence and *omic* sciences), addressing the state of the art of how its have been used to predict the success of dental implants.
2. To review how the molecular point-of-care (PoC) tests currently available can help in the early detection of peri-implant diseases.

3. To identify a test kit commercially available and approved on European Union that are already been validated to function with peri-implantitis biomarkers and that use oral fluid to diagnose.
4. To investigate dentists' perception of the implementation of a tool to support peri-implant risk assessment.
5. To create a usability test to identify improvements that can be made to the IDRA tool.
6. To create a proposal tool to predict the success of dental implants.

3 OBJETIVOS Y JUSTIFICACIÓN

La medicina de precisión es un enfoque relativamente nuevo e innovador que comienza a implementarse en odontología, habiendo dado un paso importante con la implementación de biomarcadores en la nueva clasificación de periodoncia y condiciones periimplantarias.

Varios campos de la odontología pueden aprovechar esta metodología, sin embargo, el que más destaca es la rehabilitación oral implantosoportada debido a la etiología multifactorial del fracaso del implante, como el fracaso de la osteointegración, la mucositis o la periimplantitis. Actualmente se conocen numerosos factores asociados a estas condiciones clínicas, así como los protocolos utilizados en el diagnóstico y tratamiento de estas patologías. Sin embargo, esta metodología solo es capaz de identificar la patología cuando ya está instalada, y no antes de que haya daño tisular. Es necesario introducir estrategias bioinformáticas, combinando inteligencia artificial y ciencias ómicas, en protocolos clínicos convencionales ampliamente utilizados y conocidos por los odontólogos, aumentando la precisión de la detección temprana de enfermedades periimplantarias y periodontales, la predicción de la progresión de la enfermedad y el seguimiento de los efectos del tratamiento.

Los objetivos específicos de este estudio fueron:

1. Revisar la literatura sobre bioinformática (inteligencia artificial y ciencias ómicas), abordando el estado del arte de cómo se ha utilizado para predecir el éxito de los implantes dentales.

2. Revisar cómo las pruebas moleculares en el punto de atención (PoC) actualmente disponibles pueden ayudar en la detección temprana de enfermedades periimplantarias.

3. Identificar un kit de prueba comercialmente disponible y aprobado en la Unión Europea que ya haya sido validado para funcionar con biomarcadores de periimplantitis y que utilice fluido oral para diagnosticar.

4. Investigar la percepción de los dentistas sobre la implementación de una herramienta para apoyar la evaluación del riesgo periimplantario.

5. Crear una prueba de utilidad para identificar las mejoras que se pueden realizar en la herramienta IDRA.

6. Crear una herramienta experimental para predecir el éxito de los implantes dentales.

4 ORIGINAL PUBLICATIONS

4.1 PAPER 1

BORNES RS, MONTERO J, CORREIA ARM, ROSA NRDN. USE OF BIOINFORMATIC STRATEGIES AS A PREDICTIVE TOOL IN IMPLANT-SUPPORTED ORAL REHABILITATION: A SCOPING REVIEW. J PROSTHET DENT. 2023 FEB;129(2):322. E1-322.E8.

THE JOURNAL OF PROSTHETIC DENTISTRY

SYSTEMATIC REVIEW

Use of bioinformatic strategies as a predictive tool in implant-supported oral rehabilitation: A scoping review

Rita Silva Bornes, DMD, MSc,[a] Javier Montero, DMD, PhD,[b] André Ricardo Maia Correia, DMD, PhD,[c] and Nuno Ricardo das Neves Rosa, PhD[d]

ABSTRACT

Statement of problem. The use of bioinformatic strategies is growing in dental implant protocols. The current expansion of Omics sciences and artificial intelligence (AI) algorithms in implant dentistry applications have not been documented and analyzed as a predictive tool for the success of dental implants.

Purpose. The purpose of this scoping review was to analyze how artificial intelligence algorithms and Omics technologies are being applied in the field of oral implantology as a predictive tool for dental implant success.

Material and methods. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews checklist was followed. A search strategy was created at PubMed and Web of Science to answer the question "How is bioinformatics being applied in the area of oral implantology as a predictive tool for implant success?"

Results. Thirteen articles were included in this review. Only 3 applied bioinformatic models combining AI algorithms and Omics technologies. These studies highlighted 2 key points for the creation of precision medicine: deep population phenotyping and the integration of Omics sciences in clinical protocols. Most of the studies identified applied AI only in the identification and classification of implant systems, quantification of peri-implant bone loss, and 3-dimensional bone analysis, planning implant placement.

Conclusions. The conventional criteria currently used as a technique for the diagnosis and monitoring of dental implants are insufficient and have low accuracy. Models that apply AI algorithms combined with precision methodologies—biomarkers—are extremely useful in the creation of precision medicine, allowing medical dentists to forecast the success of the implant. Tools that integrate the different types of data, including imaging, molecular, risk factor, and implant characteristics, are needed to make a more accurate and personalized prediction of implant success. (J Prosthet Dent 2023;129:322.e1–e8)

The growth of population and of increased lifespan has meant that more people are looking for treatments and solutions for lost teeth, resulting in an increased demand for bone regeneration treatments and oral rehabilitation techniques for elderly patients with specific health conditions.[1,2] Patient-related conditions, such as smoking habits, poor oral hygiene, infectious processes, systemic diseases (osteoporosis, diabetes mellitus), and drugs that affect bone metabolism, might influence the progress of bone regeneration and, consequently, the osseointegration of dental implants.[3,4] In addition, factors related to the surgical and prosthetic phase, as well as the inherent characteristics of dental implants, such as wettability, porosity, roughness, may influence the osseointegration process.[5,6]

In the approximately 40 years since the introduction of implants into clinical practice, many complications have been reported, including the loss or fracture of prosthetic dental screws, fracture of the dental implant, and biologic problems such as peri-implant mucositis or peri-implantitis.[7-9] According to Benakatti et al,[7] "dental implants will need maintenance as long as they remain in the patient's oral cavity." Therefore, information about

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Clinical Implications

The combination of both AI algorithms and Omics expertise can provide an extremely powerful tool to support the clinician's opinion, not only in terms of identifying implant systems but also in predicting implant success.

Table 1. Research methodology on PubMed (MESH)

#1	"Dental Implants"[MeSH Terms]
#2	"Artificial Intelligence"[MeSH Terms]
#3	"Precision Medicine"[MeSH Terms]
#4	"Computational Biology"[MeSH Terms]
#5	"Biomarkers"[MeSH Terms]
Research combination	#1 AND #2; #1 AND #3; #1 AND #4; #1 AND #5
Total number of articles	241 articles

the rehabilitation, including the implant system used, fixation method, and abutment used, is needed. Patient history and radiographic examination provide information that allows the clinician to identify the implant system. However, the patient's history is not always accessible, and the identification of the implant system through radiographic examination requires effort and experience.[8-12]

The development of methodologies able to integrate all the factors and predictors is possible with the use of artificial intelligence (AI). These strategies support the prognosis of the implant, predicting eventual clinical conditions such as early bone loss, mucositis, or peri-implantitis.[10,13-15] In addition, when using methods based on advanced neural networks—machine learning—it is possible to foresee the complexity and potential risk involved during the process of oral rehabilitation of the dental implants.[16,17]

The scientific evidence, as well as the assessment tools used in contemporary practice, has been based on clinical, analytical, and radiographic parameters which provide the clinician with limited therapeutic guidelines to deal with the multifactorial complexity of the implant-supported rehabilitation procedures.[18,19] Furthermore, for diagnosing and staging peri-implant disease, such methods can only register the actual tissue destruction rather than current disease activity. Moreover, those conventional strategies do not consider systemic conditions, which may influence the local immunological response, either around a tooth area (periodontitis) or around a dental implant area (peri-implantitis).[18-22]

Currently, the role of pathogens and their influence on periodontal and peri-implant diseases have been well described,[14,20,21,23,24] and it has been reported that oral dysbiotic status is necessary to trigger these pathologies.[14,20,21,23,24] This understanding has allowed the identification and confirmation of several individual conditions such as risk factors with immunological impact.[23] By considering all these facts, it is possible to create a standard clinical protocol supported by Omics technologies such as proteomics.[23] Omics technologies have emerged as a powerful tool for investigating different molecular mechanisms between health and disease states, for discovering molecules (biomarkers) commonly used in medicine to objectively determine the state of the disease or responses to a therapeutic intervention, and for identifying the targets of new therapies.[23,25]

The Omics methodology is key to the introduction of precision medicine into dentistry, especially in the field of oral rehabilitation, because it can adapt the procedure to follow in light of the patient's biological, social, and lifestyle characteristics.[26] A major goal is to reduce diagnostic mistakes, to develop results, to avoid unnecessary collateral effects, and to clarify why one individual can develop peri-implantitis and others with similar conditions did not.[23,26]

This scoping review aimed to analyze how bioinformatics have been used to predict the success of dental implants and to determine whether studies in which Omics technology have been integrated as a clinical support tool are available.

MATERIAL AND METHODS

The methodology described in the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist[27] was followed, and the research protocol was registered in the Open Science Framework (OSF) under doi: https://doi.org/10.17605/OSF.IO/XMDHR reviewed and approved by 2 experienced research professionals (A.C., R.B.). The focal question was "how are bioinformatics being used in the field of oral implantology as a predictive tool to ensure implant success?"

A search was carried out on PubMed and on the Web of Science databases with the search strategy in Tables 1-3. In each database, the search was adapted to its characteristics by combining the Boolean operators (AND, OR) with different mesh terms (PubMed) or natural language (Web of Science). All articles used were stored in a bibliographic reference manager library (Zotero), and duplicate articles were removed.

The selection of studies was based on the selection criteria and focus question (Table 4). After excluding duplicate articles, the remaining articles were selected by reading their titles and abstracts. Lastly, the full text of all imported studies was evaluated in detail by 2 reviewers (A.C., R.B.), who individually screened the articles by considering the inclusion and exclusion criteria. Any

Table 2. Research methodology on PubMed (natural language)

(Dental Implants Survival) and (Biomarkers)	
("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields]) AND ("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]) AND ("biomarker s"[All Fields] OR "biomarkers"[MeSH Terms] OR "biomarkers"[All Fields] OR "biomarker"[All Fields])	
(dental implants success) AND (biomarkers)	
("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields]) AND ("success"[All Fields] OR "successes"[All Fields] OR "successful"[All Fields]) AND ("biomarker s"[All Fields] OR "biomarkers"[MeSH Terms] OR "biomarkers"[All Fields] OR "biomarker"[All Fields])	
(dental implants) AND (biomarkers)	
("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields]) AND ("biomarker s"[All Fields] OR "biomarkers"[MeSH Terms] OR "biomarkers"[All Fields] OR "biomarker"[All Fields])	
(dental implants) AND (artificial intelligence)	
("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields]) AND ("artificial intelligence"[MeSH Terms] OR ("artificial"[All Fields] AND "intelligence"[All Fields]) OR "artificial intelligence"[All Fields])	
(dental implants) AND (bioinformatics)	
("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields]) AND ("bioinformatical"[All Fields] OR "bioinformatically"[All Fields] OR "computational biology"[MeSH Terms] OR ("computational"[All Fields] AND "biology"[All Fields]) OR "computational biology"[All Fields] OR "bioinformatic"[All Fields] OR "bioinformatics"[All Fields])	
Total number of articles	552 articles

Table 3. Research methodology on Web of Science

(Dental Implants) and (Artificial Intelligence)	
(dental implants) AND (computational biology)	
(dental implants) AND (precision medicine)	
(dental implants) AND (biomarkers)	
(dental implants) AND (bioinformatica)	
(dental implants survival) AND (biomarkers)	
(dental implants success) AND (biomarkers)	
Total number of articles	818 articles

Table 4. Inclusion and exclusion criteria of articles

Exclusion Criteria	Inclusion Criteria
Comparative microbiological technique studies with no relevance for topic	AI strategies, deep learning, and machine learning
Precision of digital printing techniques or traditional dental implant techniques	Tree model decision tools, support vector machine, or convolutional neural network
Precision in printing 3D surgical guidelines	Studies which apply Omics sciences as predictive tool to ensure success of implant
Studies that do not address Omics strategies that contribute to prediction of implant success	
Comparative and experimental studies with different dental investments/materials/design of dental implant surface or rehabilitation components	
Evaluation procedures to assess biofilm adhesion on dental implant	
Mini orthodontic implants or maxillofacial prosthetics	
Studies using animals or nonoral tissues	

differences between them were discussed with a third reviewer (N.R.), who determined the final decision.

The information was gathered from the included articles by 2 independent reviewers (A.C., R.B.), who had developed a methodology to bring together data characterized by the identification of the specific bioinformatic strategy and with regard to the clinical importance and use of that model (Table 5).

RESULTS

A total of 1611 articles were identified on the PubMed and Web of Science databases, and duplicates were removed, leaving 1011 articles. After reading the title and abstract and applying the inclusion and exclusion criteria (Table 4), the total was reduced to 47 articles. After reading the full text, a further 31 were excluded for lack of focus or not answering the focus question, leaving 16 as part of this scoping review (Fig. 1). The Cohen Kappa coefficient defined an achievement level of 84% between investigators.

Figure 1 and Tables 5-7 illustrate the role played by bioinformatics, AI, and Omics as predictive tools in oral implantology during the different phases of oral rehabilitation. Figure 2 shows a word cloud diagram where all the highlighted keywords are differently sized considering their frequency of use in the articles. The words displayed in the largest font were those used most frequently in the 16 articles. The most used words were artificial intelligence, deep learning, machine learning, and convolutional neural networks when combined with other words, including peri-implantitis, dental implant, and biomarkers, showing that studies using bioinformatic models to support clinical decisions in the field of oral implantology are available.

DISCUSSION

During the past 5 years, and especially after 2020, the number of publications on the use of bioinformatic

Table 5. Methodology used in oral implantology: Bioinformatic techniques versus conventional techniques

Article Identification	Bioinformatic Techniques: Omics Strategies	Bioinformatic Techniques: AI Strategies	Conventional Techniques: Clinical Exam	Conventional Techniques: Radiographic Exam
A deep learning approach for dental implant planning in cone beam computed tomography images[31]	–	X	X	X
A pilot study of a deep learning approach to detect marginal bone loss around implants[32]	–	X	X	X
Artificial intelligence applications in implant dentistry: A systematic review[33]	–	X	–	–
Biosensor and lab-on-a-chip biomarker identifying technologies for oral and periodontal diseases[28]	X	X	X	X
Deep neural networks for dental implant system classification[8]	–	X	–	X
Diagnosing peri-implant disease using the tongue as a 24/7 detector[29]	X	X	X	X
Diagnostic charting of panoramic radiography using deep-learning artificial intelligence system[34]	–	X	X	–
The modern and digital transformation of oral health care: a mini review[35]	–	X	X	X
Efficacy of deep convolutional neural network algorithm for the identification and classification of dental implant systems, using panoramic and periapical radiographs[36]	–	X	–	X
Identification of dental implants using deep learning-pilot study[37]	–	X	–	X
Machine learning-assisted immune profiling stratifies peri-implantitis patients with unique microbial colonization and clinical outcomes[30]	X	X	X	X
Multitask deep learning model for classification of dental implant brand and treatment stage using dental panoramic radiograph images[38]	–	X	–	X
Osseointegration pharmacology: a systematic mapping using artificial intelligence[39]	–	X	–	–
Panoptic segmentation on panoramic radiographs: deep learning-based segmentation of various structures including maxillary sinus and mandibular canal[40]	–	X	–	X
Peri-implant bone loss measurement using a region-based convolutional neural network on dental periapical radiographs[41]	–	X	X	X
Machine learning for identification of dental implant systems based on shape – A descriptive study[7]	–	X	–	–

In addition to conventional techniques used in clinical practice (clinical and radiographic examination), studies in *gray* represent combination of AI tools and Omics.

models to assess implant-supported prostheses has increased. All the studies selected used AI algorithms to help clinicians in planning, diagnosis, and follow-up.

Three articles[28-30] discussed bioinformatic models that integrated AI algorithms into established identification and quantification protocols, which are often used in Omics sciences. A total of 13 articles[7,8,31-41] underlined the development of different AI algorithms, for example, machine learning, deep learning, and convolutional neural network to support clinical decision and raising precision and accuracy levels of the rehabilitation process. Of these, 6 studies[8,33,34,36-38] developed AI models for implant type recognition. Most of the articles identified used AI algorithms as a clinical support tool, as opposed to the articles which applied bioinformatic strategies by combining knowledge from AI algorithms with Omics expertise. These findings were expected since the application of strategies based on AI in the field of oral rehabilitation and the importance given to Omics sciences as a complement to a precision diagnosis are very recent.

Comparisons of efficacy were difficult among the different AI models used because of the data input or methods used in the studies reviewed. While each study attempted to standardize the collection of the radiographical images, differences among the studies were identified, including exposure (speed and contrast) and type of radiographic images (2-dimensional [2D] or 3-dimensional [3D]). Furthermore, variations on the radiographic information differed among the reviewed studies where only the implant (with a cover screw or a healing abutment) was visible on the radiograph or the radiograph also showed the prosthetic component. A comparison of studies that used bioinformatics strategies was also difficult since the methodology was completely different among the 3 included studies.

Most articles used 2D images for implant identification; clinicians generally use these to monitor the condition of a dental implant.[8,34,36-38] However, studies that used 3D images were also included. The inclusion of cone beam computed tomography (CBCT) images might aid in the development of AI for the recognition of dental implant types.[33]

Three recently published studies[28-30] in which some bioinformatic approaches were considered were identified. The main goal of these studies was to support the clinical decision in terms of the diagnosis and staging of peri-implant diseases.

Ritzer et al[29] described a diagnosis mechanism for periodontal disease that could be performed by "anyone, anywhere, anytime." This model was characterized by embedding sensors in chewing gum that contained peptide bioresponsive sensors consisting of a protease cleavable linker between a bitter substance and a microparticle. Matrix metalloproteinases in the oral cavity, as upregulated in peri-implant disease, specifically targeted the protease cleavable linker while chewing the gum, thereby generating bitterness for detection by the tongue. This line of research had many advantages: it provided a rapid and accurate diagnosis in that the

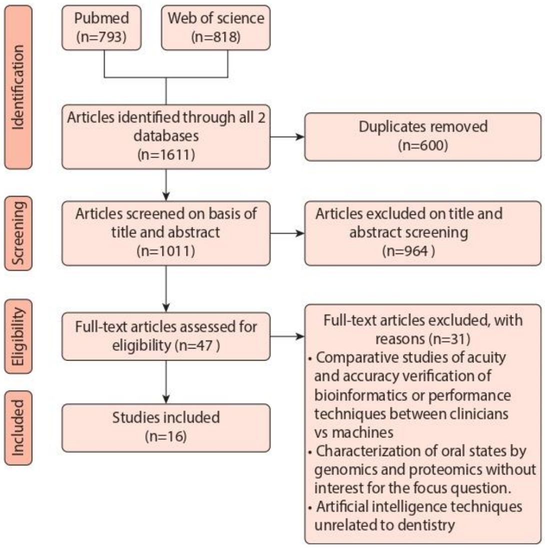

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) flow diagram for scoping review process.[21]

Table 6. Description of proposed methodology in studies which combined both bioinformatic techniques: artificial intelligence (AI) and Omics

Article	Pub. year	Proposed Methodology	Clinical Improve
Diagnosing peri-implant disease using the tongue as a 24/7 detector[29]	2017	• Developed diagnostic chewing gums	• Providing rapid read-out within few minutes.
		• “Anyone, anywhere, anytime” diagnostics.	• Saliva diagnostic.
		• Sensors responded to proteins upregulated in peri-implant disease (MMP).	• Accurate diagnosis, even before clinical evidence of disease.
Biosensor and Lab-on-a-chip Biomarker identifying Technologies for Oral and Periodontal Diseases[28]	2020	• Oral biomarkers identification	• Data processed in biosensor and AI algorithms applied to establish personal physiological thresholds and out of personal norm trends.
		• Patient stratification	• Wirelessly transferred output data supports clinical decisions during in-office or tele-dentistry appointments.
		• Bioinformatic analysis using artificial intelligence	
		• Use of biosensors to oral disease identification and risk assessment.	
Machine learning-assisted immune profiling stratifies peri-implantitis patients with unique microbial colonization and clinical outcomes[30]	2021	• Clinical, immunological, and microbiological characterization of patients diagnosed with peri-implantitis undergoing regenerative therapy.	• Relation of immune and microbiological profile for prognosis of peri-implant states and potential risk analysis tool.
		• Used artificial intelligence algorithm - machine learning.	

sensor featured a diagnosis from saliva, which removed the need to collect sulcus fluid in sites accessible only to a professional; expert knowledge in interpretation was not required; and the diagnosis could be used anywhere, in the clinic or at home. Therefore, the data provided demonstrated that the complex kits used at present may be complemented or even replaced by more straightforward and reliable chewing gum diagnosis.[24,29]

Also in 2020,[28] a model was created using advances in light-emitting diode (LED) biotechnology which enabled biosensors and microelectromechanical systems (MEMS) suitable for the oral cavity to identify and quantify molecules such as cortisol, proteins, and bacteria, permitting the uninterrupted monitoring of those molecules in human saliva. Knowledge from such testing gives clinicians the opportunity to prevent patients from developing

Table 7. Description of proposed methodology in studies which only used artificial intelligence tools

Article	Pub. year	Proposed Methodology	Clinical Interest/Clinical Improve
A deep learning approach for dental implant planning in cone beam computed tomography images[31]	2021	• Measurement of bone thickness and height in different areas of oral cavity in CBCT images by AI and by clinician	• AI results consistent with clinician's measurement in PM/M maxillary and PM mandibular areas
A pilot study of a deep learning approach to detect marginal bone loss around implants[32]	2022	• Convolutional neural networks prepared by training and validating data set by experienced dentists	• CNN detect peri-implant loss bone by using periapical radiographs.
		• Creation of AI algorithm	
Artificial intelligence applications in implant dentistry: A systematic review[33]	2021	By using AI algorithms:	–
		• Recognition of dental implant systems	• AI models recognize implant system
		• Prediction of dental implant success based on risk factors	• Models to predict osseointegration success/ implant success by using different input data
		• Optimization of dental implant design	• AI models to improve design of dental implants
Deep neural networks for dental implant system classification[8]	2020	• Recognition of implant system by using CNN	• Recognition of 11 different implant systems, despite their implant-treatment stage
Diagnostic charting of panoramic radiography using deep-learning artificial intelligence system[34]	2021	• Recognition of 10 dental states in panoramic radiograph, including dental implants	• Allows identification of oral states with no clinician intervention
Efficacy of deep convolutional neural network algorithm for the identification and classification of dental implant systems, using panoramic and periapical radiographs[36]	2020	• Identification and classification of dental implants by deep learning algorithms	• Deep CNN architecture useful for identification and classification of dental implant systems using panoramic and periapical radiographs
Identification of dental implants using a deep learning-pilot study[37]	2020	• Identification of dental implant systems using deep learning method	• Implants identified from panoramic radiographs
Multi-task deep learning model for classification of dental implant brand and treatment stage using dental panoramic radiograph images[38]	2021	• Multitask deep learning use to investigate classifier that categorizes implant brands and treatment stages from dental panoramic radiographs (implant, implant + abutment and implant + crown)	• Classification of implant brands and treatment stages by using CNNs
Osseointegration pharmacology: a systematic mapping using artificial intelligence[39]	2021	• Development of machine learning algorithm to automatically map literature assessing effect of medication on osseointegration	• Identification of effects during diagnosis of dental implants by medication that affect homeostasis, inflammation, cell proliferation, and bone remodeling
Panoptic segmentation on panoramic radiographs: deep learning-based segmentation of various structures including maxillary sinus and mandibular canal[40]	2021	• State-of-the-art deep neural network model designed for panoptic segmentation trained to segment maxillary sinus, maxilla, mandible, mandibular canal, normal teeth, treated teeth, and dental implants on panoramic radiographs	• Automatic machine learning method might assist dental practitioners to treatment plan and diagnose oral and maxillofacial diseases
Peri-implant bone loss measurement using a region-based convolutional neural network on dental periapical radiographs[41]	2021	• Deep CNN detect marginal bone level, top, and apex of implants on dental periapical radiographs	• CNN model can be used to measure radiographic peri-implant bone loss ratio to assess severity of peri-implantitis
The modern and digital transformation of oral health care: a mini review[35]	2021	• Analyses of progress, limitations, challenges, and conceptual theoretical modern approaches in oral health prevention and care, particularly in ensuring quality, efficiency, and strategic dental care in modern era of dentistry	• Digital oral scanner
			• Digital oral health records
			• Application of AR/VR and AI
			• Dynamic navigation system (DNS)
			• Static guided systems
			• Additive manufacturing
			• Tele-dentistry with remote consultation
Machine learning for identification of dental implant systems based on shape – A descriptive study[7]	2021	• Identification of dental implants in panoramic radiographs by using machine learning algorithms	• Machine learning models tested in study proficient enough to identify dental implant systems

AI, artificial intelligence; AR, augmented reality; CBCT, cone beam computed tomography; CNN, convolutional neural networks; MMP, matrix metalloproteinases; M, molar; PM, premolar; VR, virtual reality.

different pathological conditions and enables early identification of mucositis or peri-implantitis. It also allows clinicians to control the different stages of a prediagnosed pathology, preventing progression.[28]

Recently, in addition to the importance given to the accuracy of the diagnosis achieved by using the strategies Ritzer et al[29] and Steigman et al,[28] emphasis has also been given to the stratification of patients in determining the risk profile of patients and creating a consistent risk system. Wang et al[30] used a robust outliner-resistant machine learning algorithm for immune deconvolution and concluded that the peri-implant immune microenvironment shaped the microbial composition and the regeneration course. Immune signatures have shown the untapped potential in improving the risk-grading for peri-implantitis, as well as the influence of medication during osseointegration. Many patients seeking implant-supported restorations are elderly, polymedicated, or with

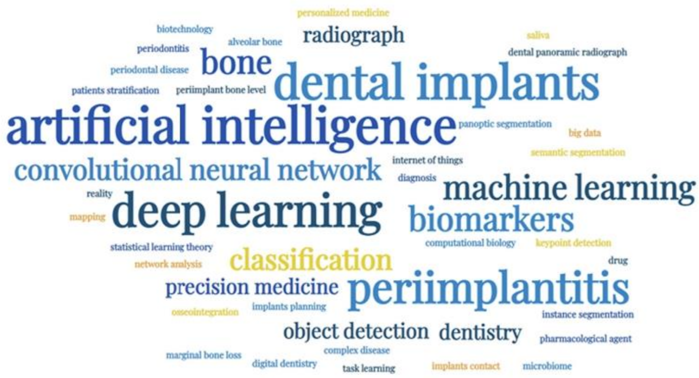

Figure 2. Representative word cloud of keywords taken from 16 articles, part of different areas of expertise being developed, as well as example of most used bioinformatic technologies so far.

comorbidities. Even though all these situations are considered during the planning period, the effect of medication during the surgical procedures is generally unclear. To precisely read and map all the process of bone integration, a machine learning algorithm has been designed to identify the influence of medications during the process, which might affect the metabolic activities involved.[39]

Alauddin et al[35] underlined the importance of scanning in dentistry, referring to limitations, challenges, and theoretical approaches for the prevention and diagnosis of oral diseases. They also mentioned that this progress has been influenced by informatic models such as augmented reality (AR) and virtual reality (VR), the internet, communication technologies, digital oral health records, digital scanners, and AI. These authors concluded that scanning might aid in AI development and in updating the systems of AI, VR, and AR and pointed out the importance of these models in dentistry to facilitate data collection and the development of different AI algorithms such as deep learning, machine learning, and neural networks.[35] Those strategies should reduce unnecessary contact between clinician and patient and shorten the duration of the treatment, which will make it more cost-effective.[35]

Importance has been given to planning oral rehabilitation, which depends on the clinician's experience and knowledge. AI systems have been used to support diagnosis and planning, and measurements from 3D images are recommended to identify anatomic variations. AI systems have been described that detect vital structures and diagnose injuries, improving implant placement and ensuring optimal oral rehabilitation.[31,40] Revilla-León et al[33] stated that cone beam computer tomography (CBCT) images could help in the development of AI models and in facilitating the recognition of dental implant systems. Using 3D images optimizes the measurement of teeth and edentulous ridges, allowing accurate planning and implant placement.[11,12,24,31,38-41] Once all the data are automatically gathered and organized in a database and then combined with the risk factors, these technologies can improve treatment precision.

Future directions in implant dentistry could combine different types of data (imaging, molecular, risk factors, and implant characteristics) to make a more accurate and clinically useful prediction of the outcome of implant-supported prostheses. Despite the relevance of identifying different implant systems and in precisely planning the oral rehabilitation procedures, creating a database which gathers all the pertinent information related to a patient's medical records (medication, pathologies, periodontal chart, and dental chart) is essential. Such a record can store data about surgical phases, prosthetic and follow-up appointments, and a wider range of biomedical information such as microbiology, proteomics, genomics, and metabolomics. Therefore, the clinician can access an early diagnosis to predict and plan the safest and most appropriate strategy to adopt and follow.[10,15,22,25]

CONCLUSIONS

Based on the findings of this scoping review, the following conclusions were drawn:

1. Both strategies analyzed (AI algorithms and Omics sciences) could be combined to create bioinformatic tools which could be integrated into clinical protocols.
2. This fusion allowed a clinical precision approach because it reduces misdiagnosis and, eventually, allows the prediction of possible outcomes.

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4.2 PAPER 2

BORNES R, MONTERO J, CORREIA A, MARQUES T, ROSA N. PERI-IMPLANT DISEASES DIAGNOSIS, PROGNOSIS AND DENTAL IMPLANT MONITORING: A NARRATIVE REVIEW OF NOVEL STRATEGIES AND CLINICAL IMPACT. BMC ORAL HEALTH. 2023 MAR 30;23(1):183.

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BMC Oral Health

REVIEW

Open Access

Peri-implant diseases diagnosis, prognosis and dental implant monitoring: a narrative review of novel strategies and clinical impact

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ABSTRACT

Background The diagnosis of peri-implantar and periodontal relies mainly on a set of clinical measures and the evaluation of radiographic images. However, these clinical settings alone are not sufficient to determine, much less predict, periimplant bone loss or future implant failure. Early diagnosis of periimplant diseases and its rate of progress may be possible through biomarkers assessment. Once identified, biomarkers of peri-implant and periodontal tissue destruction may alert the clinicians before clinical signs show up. Therefore, it is important to consider developing chair-side diagnostic tests with specificity for a particular biomarker, indicating the current activity of the disease.

Methods A search strategy was created at Pubmed and Web of Science to answer the question: "How the molecular point-of-care tests currently available can help in the early detection of peri-implant diseases and throws light on improvements in point of care diagnostics devices?"

Results The PerioSafe® PRO DRS (dentognostics GmbH, Jena) and ImplantSafe® DR (dentognostics GmbH, Jena ORALyzer® test kits, already used clinically, can be a helpful adjunct tool in enhancing the diagnosis and prognosis of periodontal/peri-implantar diseases. With the advances of sensor technology, the biosensors can perform daily monitoring of dental implants or periodontal diseases, making contributions to personal healthcare and improve the current status quo of health management and human health.

Conclusions Based on the findings, more emphasis is given to the role of biomarkers in diagnosing and monitoring periodontal and peri-implant diseases. By combining these strategies with traditional protocols, professionals could increase the accuracy of early detection of peri-implant and periodontal diseases, predicting disease progression, and monitoring of treatment outcomes.

Keywords Peri-implant diseases, Biomarkers, Molecular diagnosis, Prognosis, Precision dental medicine, Point-of-care test

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Background

Periodontitis is an inflammatory oral disease clinically characterized by pathological deepening of the gingival sulcus, loss of attachment, and formation of periodontal pockets with supportive alveolar bone resorption [1]. The beginning and development of this disease is a result of an interaction between pathogenic bacteria in the subgingival dental biofilme and the host response. In general, periodontal tissue damage is gradual, characterized by periods of active and remission disease without clearly alarming symptoms. In cases of neglect, permanent periodontal damage may occur. Although, it is well established that periodontal and periimplantar inflammation is associated with the presence of certain bacteria [2]. Additional factors and clinical confounders have been identified specially smoking, previous periodontal disease, poor oral hygiene, and residual excess cement have all been associated with peri-implant diseases [3]. Recent studies have also focused on the prosthetic features such restoration emergence profile and angle, showing that over-contoured restorations have higher risk of developing periimplantitis [4].

Early diagnosis of gingivitis or mucositis is an effective way to reduce the risk of developing periodontitis or peri-implantitis, respectively [5, 6]. The diagnosis of peri-implantar and periodontal diseases is mainly based on an array of clinical measurements and pocket probing depths, bleeding on probing and assessment of radiographic images. These clinical parameters alone are not enough to determine active peri-implant disease, future crestal bone loss, or future implant failure. Additional information based on medical records is also essential, but it does not provide information to the current state of disease activity, nor do identify the individuals who are susceptible to future disease progression [7–9]. These conventional diagnostic protocols require several manual recordings, professional examiners with trained expertise, and the clinical data refers only to established disease states, not being able to predict before clinical signs set in [10].

Recently, a consensus from the European Federation of Periodontology (EFP) and the American Academy of Periodontology (AAP) proposed a new classification of periodontal diseases that consider the disease severity, extent and progression by applying a staging and grading system [11]. One of the goals of this new classification is to develop methods for accurate diagnosis and predicting the prognosis of peri-implant disease [12]. Therefore, this new classification scheme was designed to allow incorporation of changes in line with future developments such as diagnosis based on biomarkers.

Early diagnosis of peri-implant diseases and their rate of progression may be possible with the assessment of biomarkers. Once identified, biomarkers of peri-implant and periodontal tissue destruction may alert the clinicians before clinical signs set in. Combining those strategies with traditional protocols, professionals could increase the accuracy of early detection of peri-implant and periodontal diseases, the prediction of disease progression and monitoring of treatment effects [13–15]. Therefore, it is important to consider the development of diagnostic chairside tests with specificity for a particular biomarker, indicating the current activity of the disease.

The aim of this review is to identify and analyze how the molecular point-of-care (PoC) tests currently available can help in the early detection of peri-implant diseases and throws light on improvements in point of care diagnostics devices, such as lab-on-a-chip and biosensors.

Methods

The methodology included applying a search strategy, defining inclusion and exclusion criteria, and retrieving studies; selecting studies; extract relevant data; and performing tables to summarize the results. Searches of PubMed and Web of Science were performed to gather literature published until September 2022. The search terms used follow in the Tables 1 and 2, and 3 (Supplement 1) according to the database used.

The inclusion criteria for selection were articles written in English, studies using saliva or crevicular fluid, studies which apply Omics sciences or artificial intelligence or novel approaches as predictive tool to ensure gingival, periodontal, or implant success. Exclusion criteria included any articles that failed to involve items described in the inclusion criteria or any article that described in vitro studies, studies using animals or non-oral tissues, studies using tools to predict non-implant treatment success, comparative microbiological technique studies, comparative and experimental studies with different materials design of dental implant surface or rehabilitation components.

The search strategy for this review involved 3 stages: reviewing titles, abstracts, and final selection of articles for full text analysis. Articles selected from the database search were sorted independently by 2 reviewers (R.B. and N.R.), and any differences in selection were discussed with a third reviewer (A.C.). Upon the reviewers' agreement, articles that did not meet the predetermined inclusion criteria were excluded. Abstracts of the articles selected at the second stage were independently evaluated by the same reviewers, and articles selected for final analysis were obtained in full text. At the final stage, the full text of the obtained articles was analyzed.

The need of precision diagnostic, prognostic and monitoring indicators

It is consensual in the scientific community that implant success cannot be only evaluated based on implant survival and should also consider peri-implant conditions and crestal bone-level stability. It is generally accepted that initial remodeling of peri-implant bones occurs due to the biological adaptation of peri-implant tissues, and subsequent tissue stabilization is expected [12]. The clinicians keep it as a normal bone remodeling process, however, an unstable bone can cause different problems, leaving the clinician uncertain, if the implant will be stable for longer. For this reason, clinician's duty is to seek as least bone loss as possible [16].

Peri-implantitis is an inflammatory disease that occurs in tissues around dental implants, characterized by progressive loss of supporting bone. According to the Consensus report of workgroup 4 of the "2017 World Workshop on the Classification of Periodontal and Peri‑Implant Diseases and Conditions", peri‑implant health is characterized by the nonexistence of erythema, bleeding on probing, swelling, or suppuration. It is not possible to define a range of probing depths compatible with health. Peri‑implant health can exist around dental implants with reduced bone support [2].

All the scientific evidence, as well as the clinical assessment used nowadays by clinicians is strictly based on clinical, analytical, and radiographic parameters which, indeed, provide limited information to deal with the multi-factorial complexity of implant-supported rehabilitation procedures. Furthermore, from the point of view of diagnosing and staging peri-implant diseases, those methods can only register the pre-existent state and not the current condition itself, not considering the patient's clinical condition. Moreover, it does not contemplate systemic conditions, lifestyle, hormonal changes, and ageing, among other aspects, related to individual inflammatory processes which may consequently influence the local immunological response. In other hand, for any clinician, the greatest challenge is predicting the success of rehabilitation or the identification of patients with high risk of disease [17].

In this way, there is the necessity to create diagnoses supported by precise and standardized approaches such as omics sciences. Omics technologies have emerged as a powerful tool to investigate different molecular mechanisms between health and disease states. Molecules such as biomarkers are often used in medicine to accurately determine the state of the disease or responses to a treatment and contribute to find the targets of new therapies [11, 17]. This strategy is increasingly being considered in the literature as a future protocol to be implemented in monitoring of peri-implant disease.

Thus, the peri-implant treatment would not only be an intensive local treatment and transversal to all individuals, but a more individualized treatment. This suggests a more embracing treatment, such as usual local debridement and disinfection protocols, but also give relevance to currently available systemically administered host modulation therapies. This type of protocol suggests that all patients rehabilitated with dental implants should be analyzed for well-established biomarkers systemic inflammation (for example high sensitivity C-reactive protein (hsCRP), cytokines such as interleukin-6 (IL-6), and collagenolytic enzymes such as MMP-8, MMP-9) in their biofluid samples, before and after local debridement procedures [18].

Molecular markers

Currently, we are in the "emerging era of high-integrated precision diagnostics" [19]. Although blood remains the most used biofluid sample, saliva has the potential to achieve a more relevant role on the diagnosis of pathologies. It has many advantages: it's an easy and fast collection method, and a non-invasive technique to collect the sample. As so, it may play a major role as a diagnostic biofluid especially in children and non-cooperative people [20]. Saliva has been proposed as a diagnostic fluid not only for oral diseases, such as caries, periodontitis [21, 22] and oral cancer, but also for systemic diseases, including diabetes [23], autoimmune, viral [24] bacterial and cardio- vascular diseases [15].

Literature presents several research to identify biomarkers associated with peri-implant disease. Up to the present date, different molecules have been investigated because of their molecular roles in inflammation or in tissues damage [25, 26]. Since there are numerous molecules identified in the literature related to biological mechanisms of peri-implantitis, in this study we only include the most actual, and already in use, biomarkers for peri-implantitis diagnostic point-of-care tests.

A meta-analyses that combined seven researches determined that interleukin-1beta (IL-1β) and tumor necrosis factor‑alpha (TNF-α), can be used as supplementary criteria for diagnosis of peri-implant infection, although cannot be used to distinguish peri-implant mucositis from peri-implantitis[27]. Ramseier et al. [28] reported biomarker assessment at teeth and implants in hundreds of patients 10 years after implant placement. Concerning IL-1β, it was observed significant differences between periodontal and peri‑implant conditions. Indeed, IL-1β was elevated in peri‑implantitis tissues and associated with increased probing depths. In the same study, the matrix metalloproteinase‑8 (MMP-8) demonstrated a trend similar to IL-1β, elevated in peri-implantitis and correlated with clinical parameters, such as bleeding on probing and increased probing depth [28].

Recently, Xanthopoulou et al. [29] revealed statistically significant differences of active matrix metalloproteinase-8 (aMMP-8) levels between healthy groups and the mucositis and peri-implantitis groups, and between the mucositis and the peri-implantitis groups. They demonstrated that elevated probing depths and aMMP-8 levels were significantly correlated. This information suggests that the aMMP-8 PoC test can be a helpful tool for early identification and screening of the risk of peri-implant diseases and progression. Also, Hentenaar et al. [30] compared biomarker levels in peri-implant crevicular fluid (PICF) of healthy implants with levels in PICF of implants with peri-implantitis. Levels of IL-1β and MMP-8 were significantly elevated in implants with peri-implantitis. No difference in levels of TNF-α, interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α), osteoprotegerina (OPG) and granulocyte colony-stimulating factor (G-CSF) between healthy and diseased implants was found. They also concluded that implants with peri-implantitis have higher levels of interleukin −1β (IL-1β) and aMMP-8 in PICF compared to healthy implants.

Connective-tissue degradation and loss of attachment in periodontitis and peri - implantitis diseases is due to matrix metalloproteinases. Among different matrix metalloproteinases and tissue inhibitor of metalloproteases, the aMMP - 8 has been selected as a more promising diagnostic tool [31].

Molecular tests on the market for peri-implantitis

Routine monitoring of dental implants is nowadays crucial to prevent biological complications or failures. There are guidelines and consensus that validate and standardize clinical and radiographic assessment methods for the diagnosis of peri-implant diseases [2]. Although there are no standard protocols for diagnostic molecular tests, several scientific studies suggest that such tests might be useful to identify risk factors associated with developing peri-implant diseases, thus favoring early diagnosis [15]. It is expected that these tests have a high specificity and sensitivity which could be used chairside in a dental clinic or in a home use device [13].

There is a consensus in the literature that it is necessary to implement molecular diagnostic tests using biomarkers to identify early peri-implant disease. It is considered in the literature that MMP-8 is a biomarker of significance in the new classifications of periodontitis and peri-implantitis [9, 18, 32–36]. More notably, in oral fluids MMP-8 can also serve as a predictive and preventive adjunctive biotechnological tool, avoiding or reducing the evolution of gingivitis or mucositis to periodontitis or peri-implantitis, respectively [32, 37, 38].

Recently, two PoC chairside test kits have been developed - PerioSafe® PRO DRS (dentognostics GmbH, Jena) and ImplantSafe® DR (dentognostics GmbH, Jena) - to identify the presence of active MMP-8 on the saliva samples. The kits are like a COVID test or a pregnancy test, providing two lines of results indicating a higher risk of periodontitis/peri-implantitis. The advantages of these tests are that they are inexpensive, noninvasive, do not require specialized equipment or trained staff and provide a quick result with high sensitivity and specificity [39].

Once the presence of active MMP-8 has been identified in the sample, a quantitative analysis can be performed using the PerioSafe® PRO DRS (dentognostics GmbH, Jena) and ImplantSafe® DR (dentognostics GmbH, Jena) ORALyser, which is already a commercially available quantitative reader-based on aMMP-8 oral fluid specific point-of-care/chair-side lateralflow reader-equipped immunotests[40]. The results can be both qualitative and quantitative use the ORALyser reader [9, 34, 35, 40–42].

These tests have been validated in Finland, Nigeria, Germany, Holland, Malawi, Turkey, Sweden, and USA [31, 32, 43, 44]. The tests have diagnostic sensitivity and specificity 76–90% and 96%, respectively, corresponding to odds ratio of >72 [31, 32]. The test results are quantitatively available by the reader in 5 min PoC/chair-side. The tests have been shown to be useful to screen susceptible sites and patients, differentiate active and inactive periodontitis and peri-implantitis sites, predict the future disease progression, and monitor the treatment.

The PerioSafe® PRO DRS (dentognostics GmbH, Jena) and ImplantSafe® DR (dentognostics GmbH, Jena) aMMP-8-POCT kits are efficient tools in improving the accuracy of diagnostic and prognostic of periodontal or peri-implant diseases and they are commercially available and approved technologies by the FDA on the United States of America and European Union [13, 41, 45]. PerioSafe® PRO DRS (dentognostics GmbH, Jena) and ImplantSafe® DR (dentognostics GmbH, Jena) and ORALyzer® tests have already been validated to function with a single biomarker, such as, aMMP-8 that is demonstrated as a biomarker of significance in the new classifications of both periodontitis and peri-implantitis. It is available as a mouthrinse (PerioSafe®PRO DRS (dentognostics GmbH, Jena)) and sulcular fluid/gingival crevicular fluid (ImplantSafe®DR (dentognostics GmbH, Jena)) variants [33, 35, 39–41]. The difference between both tests is that PerioSafe®PRO DRS (dentognostics GmbH, Jena) indicate the general periodontal status, whereas the ImplantSafe®DR(dentognostics GmbH, Jena) variant can be used as a site-specific test. Both have the advantage of being an easy-to-use tool-kit, and the possibility that either the patients themselves or general clinicians could interpret the result and understand whether or not they should refer the patient to a dentist [34].

Advances in point-of-care devices

Future development of these PoC test kits should ideally consider the ASSURED criteria for the characteristics of PoC devices introduced by the World Health Organization (WHO). This requires that such devices should be "affordable, sensitive, specific, user friendly, rapid, and robust, with no complex equipment and deliverable to end-users" [13].

Recently, the progress in several informatic fields especially in biotechnologies allowed the development of biosensors and microelectro-mechanical systems (MEMS). Biosensors usually contains a "bioreceptor" unit responsible for selective recognition of the target and contains a physiochemical transducer able to translate the biorecognition into a signal that are sent to reader devices via electrical signals [46]. Those devices were developed for measurements in laboratories, or in a point-of-care (PoC) settings, or even for single-use home testing [47]. However, a new PoC technology - Lab-on-a-Chip (LOC) - has been developed integrating numerous laboratory assays in a single device, including process and preparation of the sample, identifications and quantification multiple biomarkers, and analysis [48].

Noninvasive biosensors have been developed to detect target analytes in several biological fluid, such as, saliva. Wearable saliva biosensors have progressed considerably in recent decades. They start to be incorporated into dentures and then into teeth. Their application has several targets, such as dental disease monitoring, biochemical monitoring in saliva, and food intake monitoring [49]. The detect data can be transmitted wirelessly to nearby device, and then interpreted by the individual or sent directly to the clinician to check in real-time the status of his patient [50, 51].

Although there are several fields in dentistry where biosensors can be applied as real-time diagnostic strategies, such as in the identification of caries and force exerted during orthodontic treatment, nonetheless it will be discussed in detail how biosensors can help in diagnosis and monitoring of dental implants [52, 53].

Hassanzadeh et al. [52] designed a capacitive sensor to evaluate the new bone growth around the dental implant. PEEK (Poly-ether-ether-ketone) was used for the creation of the sensor and its capacitance depended on the density and growth of bone around it. During the process of bone remodeling and osseointegration, the capacitance of the sensor would gradually be reduced to a seventh of the initial value. The capacitance data was then transmitted wirelessly to the external device and converted to the readable format for dentists. The merit of this sensor is that the capacitance of the sensor is chosen as a readily detectable indicator to manifest the condition of bone anchorage all the time with low energy consumption and wireless transmission. But as a disadvantage, the sensor cannot be removed after osteointegration, therefore the potentially harmful long-term effects of the sensor should be investigated deeply [52, 53].

It is consensual that the lifetime of dental implants can easily exceed 10 years, but there are many adverse influence factors related to its biological and mechanical problems [54]. As already defined in this review, the conventional diagnosis of peri-implant diseases is based on clinical signs, which are subjective, lack precision, and are time-delayed [53]. Diagnoses and treatments out of time, allow diseases such as peri-implantitis to develop, give rise to implant failure and needs of follow-up appointments, with invasive treatments, which will bring burden and pain to patients and waste medical resources [55].

To deal with the problem of timely notice and diagnosis of peri-implant diseases, Jeffrey et al. [53] reported a dental implantable temperature sensor for monitoring peri-implant diseases and increasing the lifetime of rehabilitations. Recognizing that temperature is one of the inflammation signs, it can be a relevant indicator to monitor the peri-implant tissues. Therefore, a multi-channel temperature sensor was created based on a photo-definable polyimide. The sensor was small and flexible to adhere to the abutment of dental implants. It was shown that this sensor had high stability, repeatability, linearity, and accuracy, and can send early warning signals when peri-implant diseases occur. However, for the aim of monitoring and alerting peri-implant diseases in more than 10 years, biological security, stability and the lifetime of the sensor should be improved to identify the needs of users [53].

Furthermore, implants and prosthetic structures are connected by connection screws that can be loosed sometimes and may lead to micro-displacement between implants and prosthetic structures eventually. Such micro-displacements may also result in the failure of dental implants. To increase the rate survival of dental implants, Sannino et al. [56] proposed a system to warn micro-displacements of the implant-prostheses connection. The system consisted of a micro-displacement sensor and wireless communications that can be put inside the prostheses. The micro-displacements data was wirelessly transmitted to the external unit. This sensor not only indicated the micro-displacements of dental implants, but also provided a platform to study the loading forces of dental implants and solve other problems [57]. But the adaptability and stability of this implantable system in the oral cavity should be further studied and improved.

Dental sensors were created to monitor the dental implants and extend their survival rate. Considering the dental sensor is often integrated on dental implants and must be kept in the body for years, the stability and safety of dental sensors need further investigations.

Conclusion

Based on the findings, more and more emphasis is given on the role of biomarkers to recognize of present periodontal or peri-implantar status, as well as disease progression and response to therapy. The PerioSafe®PRO DRS (dentognostics GmbH, Jena) and ImplantSafe®DR (dentognostics GmbH, Jena) /ORALyzer® test kits, already used clinically, can be a helpful adjunct tool in enhancing the diagnosis and prognosis of periodontal or peri-implantar diseases.

In the foreseeable future, with the advances of sensor technology, the biosensors can perform daily monitoring of dental implants or periodontal diseases, making contributions to personal healthcare by the clinicians and moreover improve the current status quo of health management and human health.

Supplementary Information

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Supplementary Tables

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Authors' contributions
Rita Bornes; Javier Montero; André Correia; Nuno Rosa; Tiago Marques: Conceptualization, Methodology, Validation, Visualization, Writing- Original draft preparation, Writing - Review & Editing, Project administration.
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Publisher's Note

4.3 PAPER 3

BORNES R, MONTERO J, FERREIRA A, ROSA N, CORREIA A. DENTISTS' PERCEPTIONS AND USABILITY TESTING OF THE IMPLANT DISEASE RISK ASSESSMENT IDRA, A TOOL FOR PREVENTING PERI-IMPLANT DISEASE: A QUALITATIVE STUDY. JOURNAL OF DENTISTRY. 2023;104630

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Dentists' perceptions and usability testing of the implant disease risk assessment IDRA, a tool for preventing peri-implant disease: A qualitative study

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ABSTRACT

Introduction: we aimed to explore dentists' perceptions toward the implementation of a dental informatics risk assessment tool which estimates the risk for a patient to develop peri-implantitis.
Materials and Methods: the Implant Disease Risk Assessment Tool (IDRA) was presented to a convenience sample of seven dentists working in a university clinic, whom were asked to use IDRA with the information of three clinical cases whilst thinking aloud and then fill the System Usability Scale (SUS). A semi-structured interview technique was used with audio record to allow free expression of participants' perceptions related to the IDRA. The interviews information was categorized and analyzed by the authors.
Results: to our knowledge, this is the first study conducted to develop a qualitative usability test of IDRA, evaluating the effectiveness, efficiency, and users' satisfaction. There were more variations in responses the greater the degree of complexity of the clinical case. Generally, the participants classified the tool as good, getting usability values of 77,2 (SD 19,8) and learnability 73,2 (SD 24,5).
Conclusion: four additional factors should be considered to improve IDRA tool: 1) considering the relation between contour angle and *peri*-implant tissue height; 2) automatic periodontal classification in the IDRA tool after completing the periodontogram in the clinical software; 3) presentation of a flowchart to assist therapeutic decisions alongside the final score defined by the IDRA tool; 4) integrating of precision tests such as Implantsafe® DR… (dentognostics gmbh, Jena) and Oralyzer®(dentognostics gmbh, Jena).
Clinical Significance: etiology and pathogenesis of peri-implant diseases is multifactorial. These tools must follow a natural integration to be easily applied in a clinical setting. It is important to study their usability from the clinicians' point of view, evaluating the effectiveness, efficiency, and users' satisfaction.

1. Introduction

Peri-implant inflammation is associated with the presence of certain bacteria [1], other factors and clinical confounding variables have been identified [2]. Specifically, smoking, previous periodontal disease, poor oral hygiene, and residual excess cement have all been linked with peri-implant diseases [3]. Recent studies have also focused on the prosthetic features like restoration emergence profile and angle, showing that over-contoured restorations have higher risk of developing peri-implantitis [4].

The early diagnosis of mucositis is an effective way for decreasing the risk of developing peri-implantitis [5,6]. The diagnosis of peri-implantar diseases is mainly based on an array of clinical measurements and pocket probing depths, bleeding on probing and assessment of radiographic images. However, these clinical parameters alone are not enough to identify active peri-implant disease, future crestal bone loss, or future implant failure. Additional information based on medical records is also essential, but it does not provide information to the current state of disease activity, nor does it identify the individuals who are susceptible to future disease progression [7–9]. These conventional diagnostic protocols require several manual recordings and professional examiners with trained expertise. Also, clinical data refer only to established disease states, thus not being able to predict before clinical signs set in.

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Since the etiology and pathogenesis of peri-implant diseases have received increasing attention, a risk assessment tool was develop to predict the occurrence of peri-implantitis: the Implant Disease Risk Assessment (IDRA). This tool is used with the purpose of minimizing the chance of developing peri-implant tissue breakdown [10]. By understanding the key factors associated with the development of peri-implant diseases documented in the literature the clinician may selectively address such factors to improve the outcomes for implant therapy [11]. The analyses of results from recent studies addressing risk factors/indicators for biological complications associated with dental implants have identified eight important factors that may contribute to the development of peri-implantitis: 1) history of periodontitis; 2) percentage of sites with bleeding on probing (BOP); 3) prevalence of probing depth $\geq$ 5 mm; 4) bone loss in relation to the patient's age; 5) periodontitis susceptibility [12]; 6) supportive periodontal therapy; 7) implant restorative depth; and 8) prosthesis-related factors. These eight parameters have been combined in an octagon that helps visualizing the risk for disease development. A comprehensive evaluation using this functional diagram will provide an individual total risk profile and determine the need for measures targeting risk reduction. This new diagram was designed to allow incorporation of changes in line with future developments or additional factors become evident from the literature modifications [11].

This study aims to:

- Develop a qualitative usability test, evaluating the accuracy, sensitivity, and specificity of IDRA Tool.
- Understand the opinion of dentists regarding the implementation of clinical decision aid tools, such as IDRA.

2. Materials and methods

2.1. Study design, participants, and setting

This is a qualitative cross-sectional study followed the Consolidated Criteria for Reporting Qualitative Research Checklist (COREQ) [13]. For the present study we included a convenience population of dentists dedicated to the field of Implantology. All participants were invited to participate through an internal channel (institutional e-mails). At an early stage, two clinicians were purposively invited to participate in the study as they were qualified individuals in Dental Implants teaching in the University Catholic Portuguesa, Faculty of Dental Medicine (FMDUCP). The purpose of including especially these two clinicians was the need to verify and validate the protocol to practice with the target population. Therefore, all the described methodology was used first by these two clinicians, and after its verification and protocol improvement, it was presented to seven dentists dedicated to the field of Implantology. We believe seven individuals is adequate at the current stage of the intervention, as it yielded varied enough information to proceed on the qualitative study [14].

2.2. Procedures

The study design was divided into 1) usability testing of IDRA TOOL with think-aloud approach, 2) completion of System Usability Scale (SUS), and 3) semistructured interview with audio record as shown in Fig. 1.

To answer the first research question (What are the first thoughts, feelings or impressions of clinicians while practicing IDRA?) three clinical cases were presented to the 7 clinicians and they were asked to determine the risk of each clinical case using the IDRA tool (https://www.perio-tools.com/idra/en/). The clinical cases presented were real patients from the FMDUCP university dental clinic. For the creation of each case, text information was collected from the clinical record, together with the orthopantomography and the periogram. It should be noted that the cases follow an increasing gradient of complexity and seek to include several possible scenarios according to the tool's request (Supplement 1).

In this stage, the think-aloud approach was used. Each participant was instructed on how to think-aloud during the IDRA tool protocol intervention [15]. The goal of performing a think-aloud test is to record potential users' experiences and thoughts about this tool. The role of the principal investigator in the thinking aloud approach was to interact with the participants, guide them through the tasks, and encourage them to think aloud during the tests. The main researcher, as moderator, did not intervene or disrupt the thinking process, only if the participants actively asked for help where they guided to move forward with the tool.

After the thinking aloud, the clinicians were asked to complete the System Usability Scale (SUS) (Supplement 2). The SUS is a widely established tool within the field of usability research [16]. Its 10 items (e.g., 'I think that I would like to use this system frequently') were answered on a 5-point scale from 1 ('Strongly disagree') to 5 ('Strongly agree'). Individual overall SUS scores were determined following the procedure described by Lewis et al. [17], resulting in scores ranging from 0 to 100 in 2.5 point increments, where scores >68 were considered as above average, scores >80 as high, and 100 representing best possible usability [18]. To interpret individual SUS scores, corresponding adjectives (e.g., 'good' or 'excellent') identified by Bangor et al. [19] were added. It was chosen because of its extensive use in medical research, simplicity, and suitability for small sample sizes [18,19]. This scale was individually presented to the participants right after the first contact with the IDRA TOOL, before any discussion. The main objective of this scale is to ask participants to register their immediate response to each item, and not to deliberate the response for a long time. SUS is not a diagnostic tool. It was used to provide an overall usability assessment measurement, as defined by ISO 9241–11, which was made up to answer the following characteristics: effectiveness, efficiency, and satisfaction.

Additionally, a semistructured interview was conducted between the

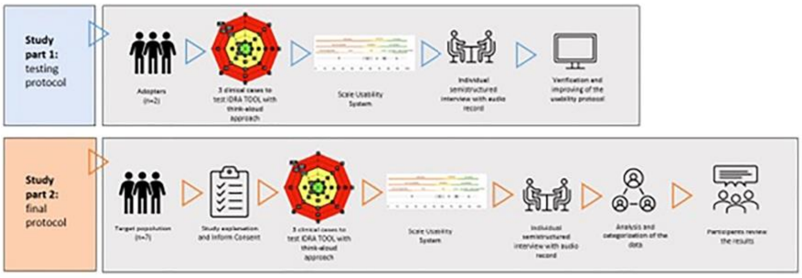

Fig. 1. Study protocol.

main researcher and participating clinicians to express their thoughts and opinions about their experience of use IDRA tool. The fact that a think-aloud method will always exclude some thought processes that are not held long enough to be expressed in working memory, a follow-up interview is commonly recommended to add in-depth information of participants thought processes and to allow interviewees to validate researchers' interpretation of their think aloud utterances [20]. Individually a discussion was conducted by the main researcher for each clinician to reflect on their perceptions toward the IDRA tool experience (Supplement 3). Those interviews were meant to answer the second research question: What are the clinicians' perceptions toward IDRA utility? The interviews were audio-recorded and then converted into English language by the principal investigator.

2.3. Data analysis

Considering the sample size, the data was processed using Microsoft Excel®(Windows). Data analysis included the listening and understanding of the audio recordings by the main researcher, and subsequently the categorization of the information into overall usability themes regarding the contents of the identified usability findings. Also, examples of each category were shown to illustrate each theme. Finally, a subsample of the participants was contacted to check and review the results. They were asked to comment if their views were totally represented and if they agreed with the authors' interpretation.

3. Results

In this section, the results from usability testing of IDRA Tool (Table 1, 2, and 3), the data collection of semistructured interview and think-aloud approach (Table 4), and completion of SUS (Fig. 2) are presented.

Table 1, 2, and 3 shows the answers given by the 7 participants when filling out the IDRA Tool. Although all the information presented to the participants was the same, the presence of variation in responses is verifiable, especially in clinical case 1 and 2. The identified themes are categorized on table 4 and to illustrate them, some examples used by the participants were summarized. To analyze the answers given by the 7 participants in the SUS, a bar graph was created (Figs. 2). The average usability rating measured via SUS was 76,4 (SD 19,2). In this study, the usability dimension had a score of 77,2 (SD 19,8) and the learnability dimension had a score of 73,2 (SD 24,5), indicating that patients perceived both usability and learnability of the IDRA Tool similarly as good [19].

4. Discussion

To our knowledge, this is the first study conducted to develop a qualitative usability test of IDRA Tool, evaluating the effectiveness, efficiency, and users' satisfaction. Overall, participants shared favorable beliefs and expectations about IDRA Tool and its ability to increase the early detection and prevention of peri-implant diseases.

Qualitative data enabled us to discover specified usability aspects as well as valuable recommendations. Accompanying interviews showed that appreciation, interest, and willingness to use were high. However, problems involving technical and clinical barriers interfered with some clinicians. Quantitative measures consisted of the usability testing protocol and the use of SUS questionnaire, wherein patients general usability rated as good (76,4), helped to identify potential issues which may eventually be improved or surpassed in a possible tool update.

4.1. Comparison of responses entered the idra tool considering think-aloud approach and the interviews

In an initial phase, it was intended to verify the first reactions and impressions of clinicians during the first contact with the IDRA Tool. The reactions obtained by the clinicians were homogeneous, reporting the tool was organized, visual and interactive (Table 4).

Regarding the first clinical case (table 1), it is verifiable that all clinicians interpreted the information presented in the same way, and therefore there was no variation in the responses inserted in the analyzed parameters of the tool. The same is not verified in the following clinical cases. Where a greater number of variations is notable especially in the third clinical case.

In the second and third clinical cases there is a variation of responses in the definition of the field "periodontitis susceptibility", which is corroborated by clinicians during the think aloud approach, where they claim that they are not familiar with the new classification of periodontitis and that only clinicians who are dedicated to the area of periodontology are able to easily identify the state and grade of periodontitis("…difficulty in classifying periodontitis"; "…requires knowledge of the new classification of periodontology…"). Some clinicians suggest the integration of IDRA tool into clinic software. After completing the periogram, the periodontal diagnosis, including state and degree of disease, could appear automatically in the tool ("Integrate this software tool so that the fields are filled in after completing the periodontogram").

Regarding the field " Number of sites with PD $\geq$ 5 mm ", there were no response variations, once necessary information was presented through a periodontal chart. Clinicians only must identify, count and register the number of sites with a probing depth equal or greater than to 5 mm. The same method was used to determine the supportive periodontal therapy.

Regarding the "% Alveolar bone loss" field, the response variations between clinicians in the second clinical case are notorious. A question that arose in this field was whether it applied to natural teeth and dental implants or only to natural teeth. Clinicians suggested that this field should be better detailed. Thus, when the tool is used, the user will have all the necessary information in the same place. In the third clinical case, as it is an edentulous patient, this field was automatically blocked, which was accepted with interest by the clinicians, once it facilitated filling out the tool, demonstrating its dynamics and interactivity between the different clinical cases ("…not having teeth, it blocks the field…"). Returning to answer variations, in the second clinical case, most clinicians answered correctly and without exposing doubts in the think aloud approach. However, 3 clinicians had doubts about how to account the bone loss of worst affected tooth site. Considering the reports of the 3 clinicians during think aloud approach, it is due to the way of identifying this bone loss, Heitz-Mayfiled et al. [11] indicate that "Bone loss is estimated from a periapical or bitewing radiograph". The

Table 1
Information referring to "clinical case 1" entered by the 7 clinicians in the IDRA TOOL.

Participants identification Diagram parameters	A1	B1	C1	D1	E1	F1	G1
Periodontitis susceptibility	Health	Health	Health	Health	Health	Health	Health
Number of sites with PD $\geq$ 5 mm	0	0	0	0	0	0	0
% alveolar bone loss	0	0	0	0	0	0	0
Supportive periodontal therapy	Compliant	Compliant	Compliant	Compliant	Compliant	Compliant	Compliant
Restorative margin to bone	Soft	Soft	Soft	Soft	Soft	Soft	Soft
Implant prothesis	Cleanable	Cleanable	Cleanable	Cleanable	Cleanable	Cleanable	Cleanable

Table 2
Information referring to "clinical case 2″ entered by the 7 clinicians in the IDRA TOOL.

Participants identification Diagram parameters	A2	B2	C2	D2	E2	F2	G2
Periodontitis susceptibility	III	III	II	III	II	II	III
Number of sites with PD $\geq$ 5 mm	2	2	2	2	2	2	2
% alveolar bone loss	50	30	20	80	80	80	80
Supportive periodontal therapy	5 months or less	5 months or less	5 months or less	5 months or less	5 months or less	5 months or less	5 months or less
Restorative margin to bone	Soft	Soft	Soft	Soft	Soft	Soft	Soft
Implant prothesis	Cleanable	Cleanable	Cleanable	Cleanable	Cleanable	Cleanable	Cleanable

Table 3
Information referring to "clinical case 3″ entered by the 7 clinicians in the IDRA TOOL.

Participants identification Diagram parameters	A3	B3	C3	D3	E3	F3	G3
Periodontitis susceptibility	5 teeth loss	III	III	IV	5 teeth loss	5 teeth loss	5 teeth loss
Number of sites with PD $\geq$ 5 mm	19	19	19	19	19	19	19
% alveolar bone loss	–	–	–	–	–	–	–
Supportive periodontal therapy	None	None	None	None	None	None	None
Restorative margin to bone	>1,5	<1,5	>1,5	<1,5	>1,5	<1,5	>1,5
Implant prothesis	Not	Not	Not	Not	Not	Not	Not

fact that there is no rigorous method of measuring bone loss, but rather an estimate, clinicians are doubtful and reticent about their answer.

There were no variations in responses to the "Implant prothesis-related factors" field and there were no doubts or difficulties by clinicians in filling it out. Nonetheless, it is necessary to choose an assessment methodology with less subjective and more personalized. In this sense, patient *compliance* should be evaluated in this vector. Since even with the best intentions and efforts by health professionals, the expected goals will not be achieved if patients do not have a certain degree of *compliance*. The aim is to measure the plaque index at each visit by means of a plaque developer and then fill in the corresponding vector. The main goal is besides recording concrete data capable of quantitatively identifying the bacterial plaque of that individual, it also works as an awareness and form of doctor-patient communication in the improvement of oral health care [21–23].

The field "Restorative margin to bone" was the one that generated the most doubts during its completion and the one that obtained the greatest variation in responses. It's consistent in the literature that the distance of ≤1.5 mm from the restorative margin of the implant-supported prosthesis to the marginal bone crest at time of restoration as a risk indicator for periimplantitis. In this sense, Heitz-Mayfiled et al. [11] created the functional diagram according to this hypothesis: low risk for a soft tissue level implant, moderate risk as a distance of 1.5 mm, and high risk as a distance of <1.5 mm [24]. However, one of the doubts raised by the clinicians was "I can answer according to the patient's current status, but I don't know how it was when the patient was prosthetically rehabilitated." This hypothesis was already considered in the IDRA Tool presentation article. However, in the clinicians' opinion, an alternative to this field should be found. The evaluated factor would be more rigorous and invariable, such as the relation between contour angle and *peri-*implant tissue height [25].

A participant also highlighted the importance of having a flow-chart to assist therapeutic decisions alongside the final score defined by the IDRA tool. Currently, Heitz-Mayfiled et at. [26] published in the 13th volume of the ITI Treatment Guide a decision support flowchart, which supports and normalizes the therapy in cases of peri-implant diseases.

Lastly, two participants mentioned the importance of integrating

Table 4
Data collection of semistructured interview and think-aloud approach.

1. What are the first thoughts, feelings or impressions of clinicians while practicing IDRA?

Theme	Example
Confidence ($n = 5$)	"I see this tool capable of optimizing my check-ups for the patients I rehabilitate"; Would recommend 100%"; "I would use this tool a lot."
Organized ($n = 1$)	"...great to have the possibility to save the file at the end of each analysis"
Visual ($n = 3$)	"...it's not confusing at all, the diagram helps to understand which factor or factors we should try to modify"
Personalized ($n = 2$)	"...we can choose how many points to probe ..."
Interactive ($n = 2$)	"...not having teeth, it blocks the field ..."

2. What are the clinicians' perceptions toward IDRA utility?

Theme	Example
Consistency with guidelines ($n = 7$)	"...more prosthetic data should be incorporated... I don't know how the patient occludes, for example"; "...it was interesting to ask the height of the prosthetic abutment."
Barrier ($n = 7$)	"...difficulty in classifying periodontitis"; "... requires knowledge of the new classification of periodontology"
Limitation ($n = 2$)	"...I can answer according to the patient's current status, but I don't know how it was when the patient was prosthetically rehabilitated."
Complexity ($n = 7$)	"simple, useful tool ..."
Systematized ($n = 3$)	"...tool that systematizes patient controls"; "helps improve patient controls"
Development ($n = 2$)	"...depending on the score that results from the tool, a kind of decision/therapeutic tree should be automatically generated to follow..."; "Integrate this software tool so that the fields are filled in after completing the periodontogram"
Scientific approach ($n = 2$)	"...genetic evaluation tests should be integrated, polymorphisms...but I don't know if it exists. I know for periodontitis, inflammatory response tests."
More training ($n = 7$)	"...has to be explained or studied before"
Aim of intervention ($n = 4$)	"...allows you to quickly identify patients at risk."
Link with clinical software ($n = 6$)	"...new classification is complex, it has to be well studied or else there is a way to have it done automatically here in the tool."
Didatic and educacional ($n = 1$)	"...an interesting tool from a didactic and educational point of view..."
Collaboration with recent clinicians ($n = 1$)	"...useful for clinicians to initiate contact with patients rehabilitated with dental implants, who still have not systematized the factors to be taken into account in the diagnosis of these pathologies."
Interact with patients ($n = 1$)	"...it generates valuable information, to be presented to the patient during the control appointments to have an objective examination and something tangible to be able to understand the state of health of the dental implants."

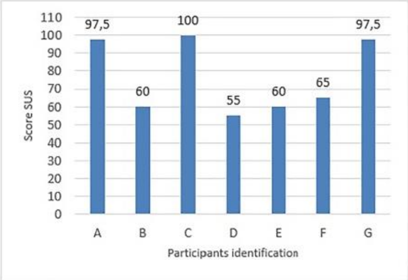

Fig. 2. Analysis of the SUS score of each participant.

precision tests into peri-implant risk tools, such as genetic tests or tests for inflammatory mediators. ImplantSafe® DR… (dentognostics GmbH, Jena) and ORALyzer® (dentognostics GmbH, Jena) tests have already been validated to function with a single biomarker, such as, aMMP-8 that is demonstrated as a biomarker of significance in the new classifications of peri-implantitis. These tests could be integrated into risk assessment tools with two main objectives. One with short-term results: identification of imbalances in the amount of aMMP-8 and consequently the early detection of peri-implant diseases, even before there are clinical signs. Another objective would be the creation of a database that gathered clinical and molecular data that in the long term would enable new lines of investigation and development of new approaches in diagnosis and therapy [27–32].

Although not mentioned by any of the clinicians surveyed, great importance has been attributed to the thickness of keratinized peri-implant mucosa to ensure long-term peri-implant health. Historically, classic studies attributed minimal importance to the peri-implant soft tissue conditions. Heitz-Mayfield, in a systematic review for the Sixth European Workshop on Periodontology found "no association between the absence of keratinized peri-implant mucosa and peri-implant disease" [33]. Later, Esposito et al. [34] stated that there is "insufficient reliable evidence to provide recommendations whether techniques to increase the width of keratinized/ attached mucosa are beneficial to patients or not". In the same period, Wennstrom and Derks [35] during the third EAO Consensus Conference found out that the evidence in support of the need for keratinized tissues around implants to maintain health and tissue stability is limited. In more recent years, the attention of the scientific community over the importance of soft tissues has dramatically increased as demonstrated by the great number of systematic reviews published in a short period of time: in particular, Gobbato et al. [36] found out that reduced keratinized mucosa width (KMW) around implants appears to be associated with clinical parameters indicative of inflammation and poor oral hygiene, suggesting the need of a certain amount of keratinized thickness to guarantee peri-implant health. In the same years, similar conclusions were drawn by Lin et al. [37] and Brito et al.60 who found that lack of adequate keratinized mucosa (KM) around endosseous dental implants is associated with more plaque accumulation, tissue inflammation, mucosa recession, and attachment loss. In 2021, the EAO organized the sixth Consensus Conference. Fickl et al. [38] investigated the influence of soft tissue augmentation procedures around dental implants on marginal bone level changes and found out that soft tissue augmentation either for augmentation of keratinized mucosa or soft tissue volume inconsistently influenced marginal bone level changes when compared to no soft tissue augmentation, but consistently improved secondary outcomes such as bleeding indices, mucosal inflammation, and peri-implant pocket depth. The combination of soft and hard tissue augmentation showed no statistically significant difference in terms of marginal bone level changes when compared to hard tissue augmentation alone but resulted in less marginal soft tissue [39]. Similar results have been published in the same period following the 2022 DGI, Osteology Foundation, and SEPA by Ramanauskaite et al. [40] who stated that, based on the observation that significantly less bone loss occurs around implants placed in thick tissue phenotypes com-pared to thin phenotypes, clinicians may be encouraged to augment thin, soft tissue before or during implant placement to enhance crestal bone stability. One of the remaining open questions is whether specific clinical thresholds in soft tissue thickness should be used to distinguish be-tween peri-implant health and disease: as reported by Ravida et al. [41] the presence of KM is not essential to achieve peri-implant health, but the quality of evidence supporting KM as a risk factor for peri- implant disease and the 2-mm cutoff point used in the literature is low at best. Very recently, Tavelli et al. [42] reported that implant sites characterized by the presence of KM were associated with a high stability of the peri-implant soft tissue margin. Two factors may have influenced the results of this literature research. First, different thresholds were used by different researchers to define an adequate width of KM to maintain peri- implant health. From a clinical perspective, the presence of a soft tissue seal around the collar of the implant, regardless of the dimensions, works as an effective barrier, capable of biologically protecting the peri-implant structures still seems of paramount im-portance. In this regard, it may be reasonable to suggest that an absence of KM and the presence of a thin (0–2 mm) band of keratinized tissue should be considered to represent two different clinical conditions, even though they were included in the same group, in several studies. The other important factor that could explain the lack of association between paucity of KM and peri-implantitis, is that the incidence of peri-implantitis increases with time. Therefore, to demonstrate a possible association, we would need several long-term studies, when instead most of the research on this topic is limited to a few years of follow-up [43–45].

Likewise, Rocuzzo et al. [46] demonstrated the presence of one or two adjacent teeth seemed to have no impact on peri-implant marginal bone level changes, rejecting scientific hypothesis that periodontal attachment of a tooth adjacent to a dental implant plays a beneficial role in maintaining the peri-implant marginal bone level [47].

4.2. Comparison sus considering think-aloud approach and the interviews

In Fig. 2, it is possible to verify the results of the questionnaire completed by all participants.

Generally, in Fig. 2, the SUS score of each participant can be observed, with the divergence of results in 2 groups being notorious: a group with a score between 97.5 and 100, and another group with a score between 55 and 65. This duality represents the feedback given by clinicians during the individual semi-structured interview. On the one hand, there were clinicians who mentioned positive points such as "… tool that systematizes patient controls", "helps improve patient controls" and "…allows you to quickly identify patients at risk". In the opinion of these clinicians, it is a clinical decision support tool, which helps not only to systematize the factors to be considered during the control consultations of patients rehabilitated with dental implants, but also helps to quickly identify, with only 8 factors, the risk of peri-implantitis of a given patient. On the other hand, some clinicians consider this tool interesting for young dentists who are starting to get in touch with the area of oral implantology, so with this tool they will be able to have the parameters that they should consider to evaluate the risk of a patient developing a peri-implantitis. The same participants also mention the interest of this tool for explaining to the patient their risk of developing a peri-implant disease, showing through the functional diagram which parameters can be modified to alter the risk.

4.3. Limitations

The conceptual and exploratory nature of this study implies less statistics and have left most of the data up for personal interpretation by the researcher. Even though the intentions have been to avoid it, the potential bias should not be underestimated.

5. Conclusions

Based in these findings, future efforts should focus on improving and standardizing protocols and reporting of prediction modeling in peri-implant diseases, conducted to implementation of validated models in clinical practice, measuring their utility and considering new sources of predictors.

Ultimately, through this usability test study of the IDRA tool, it is agreed that the following 4 aspects should be considered:

- Considering the relation between contour angle and *peri*-implant tissue height;
- Automatic periodontal classification in the IDRA tool after completing the periodontogram in the clinical software;
- Presentation of a flowchart to assist therapeutic decisions alongside the final score defined by the IDRA tool;
- Integrating the results of precision tests such as Implantsafe® DR… (dentognostics gmbh, Jena) and Oralyzer®(dentognostics GmbH, Jena).

CRediT authorship contribution statement

Rita Bornes: Conceptualization, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing, Project administration. **Javier Montero:** Conceptualization, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing, Project administration, Supervision. **Ana Ferreira:** . **Nuno Rosa:** Conceptualization, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing, Project administration, Supervision, Funding acquisition. **André Correia:** Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing, Project administration, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jdent.2023.104630.

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5 DISCUSSION

5.1 THE NEED TO CREATE AN INTEGRATIVE DATABASE

Throughout the years, dental implants have become the most searched solution for the rehabilitation of edentulous areas. It is a restorative alternative that can return patient's function and esthetics. However, biological, mechanical and technical complications are inevitable in face of the dynamics of the stomatognathic system. Consequently, these complications may compromise the success of the rehabilitation. Concerning all the questions related to implantsupported oral rehabilitation, there are several studies that have tried to give a credible and effective answer to some of these questions (28,32–34,78,79).

Our literature review on the use of bioinformatic strategies as a predictive tool in implant-supported oral rehabilitation indicated their applicability in several domains. The example of how *omics* sciences can be implemented in clinical protocols for the maintenance of dental implants to help in the early diagnosis of peri-implant diseases and how different artificial intelligence algorithms, such as conventional neural networks, deep learning, and, machine learning can help in the creation of clinical decision support tools.

All these applications are particularly relevant in this era, where the role of artificial intelligence as a support for everyday activities is increasingly highlighted. In this sense, according to our literature review on this topic, it is certain that there will be an exponential growth of tools that integrate this type of strategies capable of supporting any clinical decision.

Most of the articles selected are related to planning and maintenance of peri-implant health. These two phases of oral rehabilitation are the most relevant for the clinical success and the ones that should be the most bioinformatically supported. The rehabilitation's success presupposes an adequate planning, as well as an appropriate follow-up, aiming the early detection of any technical or biological complication.

According to the data analyzed, most of the studies were related to the identification of the dental implant system through 2D radiographs. However, the authors recognize this two-dimensions as a limitation and point to future studies the use of three-dimensional images, while other studies are already designing algorithms for three-dimensional images analyzes(33,80–84). However, algorithms are also being created to identify marginal bone loss and the success of osseointegration of the implant, based on the presence of risk factors of the patient (81,85,86). These advances allow clinical diagnoses to become more rigorous, since they do not depend on the subjectivity inherent in conventional clinical protocols, but on accurate AI algorithms. However, both conventional and AI models can only recognize a peri-implant pathology when it is already installed, evaluating the severity of the pathology through measurements. Is it possible to diagnose these conditions before they set in? Is it possible to accurately predict peri-implant prognoses? These are some questions that arise, and which make it imperative to create a methodology that obeys the assumptions of precision medicine.

The starting point of this process is the deep phenotyping of individuals. This phase consists of collecting individual patient data at different levels, from the simplest to the most complex data. Therefore, data regarding medical history, lifestyle, physical examinations, basic laboratory tests, radiographic images and data obtained through omics sciences must be collected (figure 4). Currently, *omic* sciences, especially genomics and proteomics, have aroused interest in the scientific community as they allow identifying molecular differences among individuals, which can explain many of the clinical variations/responses. Allowing to answer questions such as: How is it, that patients with equal clinical conditions, some develop peri-implantitis, while others do not?

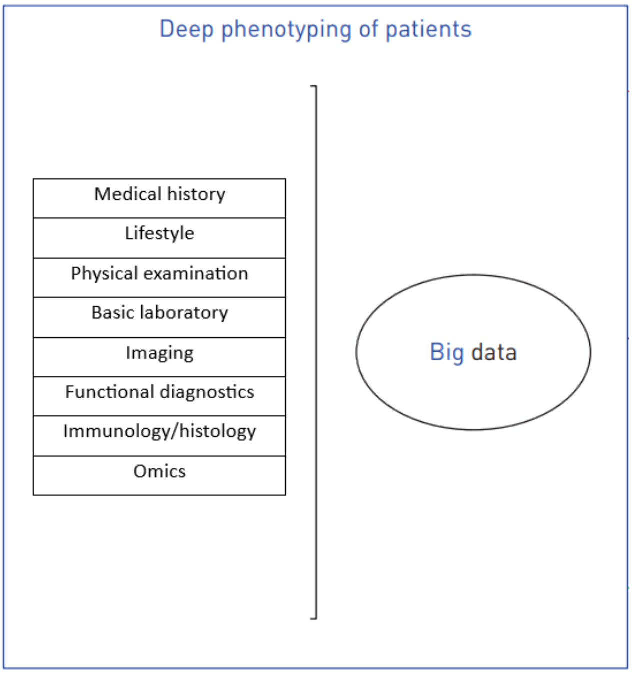

Figure 4: Deep Phenotyping of Patients (Adapted from Konig IR et al. (2017)(45))

Therefore, it is crucial to implement molecular point-of-care (PoC) tests in new clinical protocols, namely in those used during follow-up visits where the risk of a patient developing peri-implantitis is assessed. Thus, a second review was performed to identify and analyze how the molecular PoC tests currently available can help in the early detection of peri-implant diseases, identifying which PoC tests could be incorporated into this new clinical methodology for peri-implant risk assessment.

5.2 POTENTIAL POC FOR PERI-IMPLANTAR FOLLOW-UP

Point-of-Care technology aims to evaluate the levels of biomarkers that have shown to be associated with the disease *status*. These tests have already been used in general medicine for blood coagulation, immunological, and cardiovascular biomarkers. Moreover, some of these tests, such as pregnancy tests and for blood glucose levels, are available for home use(87). There is potential for developing further PoC tests in medicine, and the World Health Organization (WHO) has introduced the ASSURED criteria for the characteristics of PoC devices. This stipulates that such devices should be “affordable, sensitive, specific, user friendly, rapid, and robust, with no complex equipment and deliverable to end-users” (88). These kits have mainly been used to determine levels of biomarkers in oral fluids. Molecules, such as enzymes (bacterial and host enzymes), mediators of inflammation, and extracellular matrix components that represent the alteration of periodontal tissues have been investigated (89,90). Amongst the molecules, enzymes (MMP8 in particular) have been mainly examined and translated as chair side tests. Generally, these tests are not widely used in the clinic because of complex procedure, low sensitivity and specificity (89), whereas, the more recently developed PoC test kits, namely PerioSafe® and ImplantSafe®, can provide results within 5–7 min, with sensitivity and specificity of 76.5% and 96.7%, respectively (91,92).

Matrix metalloproteinases (MMP) family members are enzymes mainly responsible for degrading all extracellular matrix and basement membrane proteins during physiologic remodeling(93). During disease, MMP8 is one of the major collagenolytic enzymes highly involved in the destruction of periodontal/peri-implant tissue and progression of periodontitis/peri-implantitis(94). The level of MMP8, in particular, were markedly upregulated in proportion to the severity of disease, which potentially makes it possible to measure and accurately reflect the past, current, and anticipated clinical condition(95,96). Recently, the effectiveness of PoC/chair-side testing using saliva, GCF, PISF, and mouth rinse has been comprehensively reviewed(97).

MMP8 is present in oral fluids in detectable amounts that can provide clinically significant and meaningful readings. The main source of this collagenase is degranulated polymorphonuclear leukocytes (PMN) cells, which release up to 20% of their content as MMP8(98). Although PMNs are the major contributors of MMP8, this collagenase can be derived from other non-PMN lineage sources, including fibroblasts, epithelial cells, endothelial cells, macrophages, and smooth muscle cells(98–100). The salivary MMP8 is derived from PMNs leaking from gingival sulcus to the oral cavity rather than being secreted by major salivary glands (figure 5) (101). This notion is supported by the high resemblance of the amount of MMP8 was significantly reduced in edentulous subjects when compared to dentate individuals(102).

Pathologically involved peri-implant sites showed a similar pattern of elevated MMP8 level in PISF to that observed in periodontitis sites(103–105), with a similar cellular source being mainly derived from inflammatory cells, particularly PMNs (figure 5)(105). Increased severity of bone loss and osteolytic activity during peri-implantitis was found to be associated with the aMMP-8 level in PISF(105), which was further confirmed by another study(106). Results from a 10 years retrospective analysis, showed a positive correlation between upregulated MMP8 expression in GCF and PISF, and the degree of inflammation(102). Similar to the natural dentition, the response of tissues supporting dental implants to treatment can be predicted by measuring aMMP-8 levels in oral fluids (99).

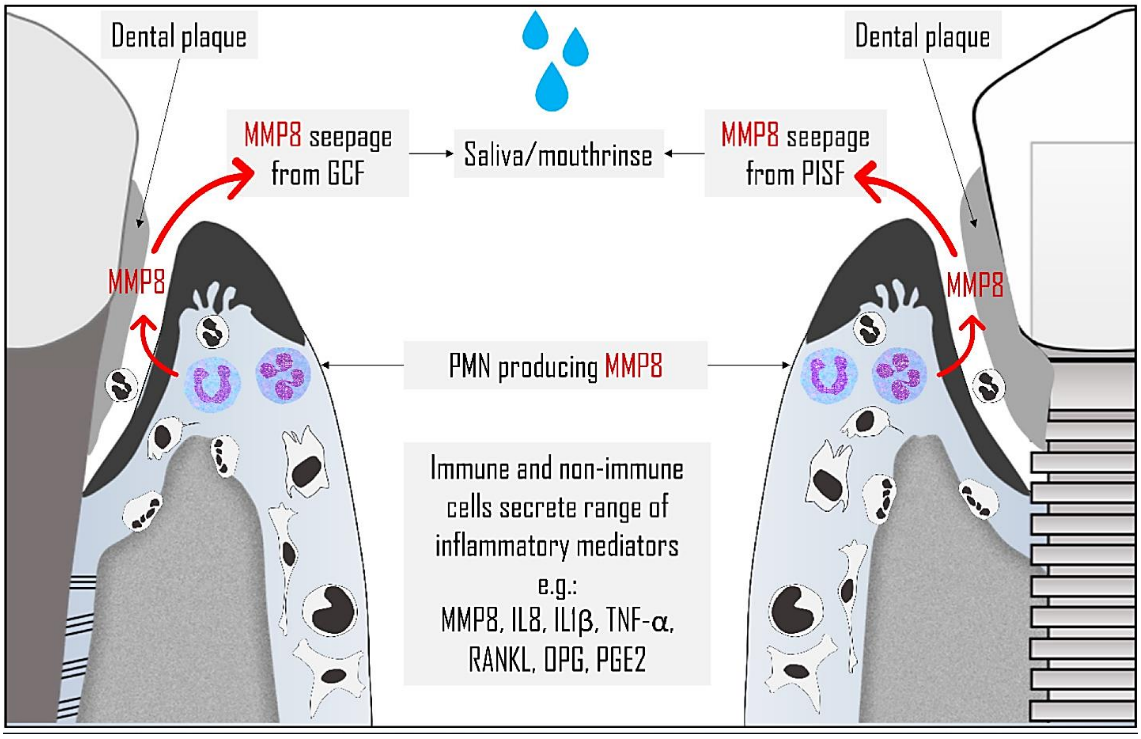

Figure 5: Sources of matrix metalloproteinase (MMP) 8 in oral fluids (adapted from Sarhang et a.l (2020)(88)).

The presence of pathogenic bacteria, mainly red complex group, in the dental biofilm stimulates production of a range of cytokines, such as tumor necrosis factor-α (TNF-α), IL1β, and MMP8, through Toll-like receptor (TLR) signaling downstream (107,108). Among periodontal pathogens, *Treponema denticola* (*T. denticola*) and *T. forsythia* were found to have the potential to induce the inflammatory cascade associated with increased expression of MMP8 (109). In addition, *T. denticola* and *P. gingivalis* proteases are able to directly activate human pro-collagenases, by converting latent MMP8 into its activated form (110).

In health, MMP8 in oral fluids is substantially in its idle form, while the expression of the activated form increases in response to periodontal/peri-implant conditions (100,111). The activity, severity, progression, and response to the treatment of these conditions were found to be significantly and positively associated with the position of aMMP8 (92,94). Presently, MMP8 based assays are available as chair- side kits that are sensitive, time- saving, specific and accurate in differencing periodontal health and disease. Indeed, introduction of an MMP8 based point-of-care test that utilizes saliva as a platform for periodontal assessment testing is a “ game changer ” that not only provides data about the current situation but also identifies susceptible individualities and predict the success of treatment (94,96,112).

Table 1 summarizes some studies that used PoC aMMP8 chair-side tests to examine peri-implant health and disease in oral fluids, as well as that produced promising results in clinical practice. This table summarizes, in a visual way, the information of several studies that have investigated the use of MMP8 by different assays for peri-implant diseases and which indicate the efficiency of this biomarker in different aspects related to diagnosis and prediction of treatment outcomes.

Table 1: Summary of studies that used point-of-care (PoC) aMMP8 chair-side tests to examine oral fluids for peri-implant health and disease.

AUTHOR	AIM(S)	STUDY GROUPS	ORAL FLUID EXAMINED	POC/CHAIRSIDE TEST	CLINICAL CRITERIA	RESULTS
Ritzer *et al*., 2017(106)	Determine the efficiency of sensory chewing gums as 24/7 detector to differentiate between patients with peri-implant disease and healthy subjects	Peri-implantitis or mucositis group and healthy volunteers	PISF, Unstimulated saliva	aMMP-8 levels were assayed by DentoELISA, Dento-Analyzer, and peptide sensor (PCL ID #1c)	N/A	Level of MMP8 was significantly higher in patients with peri-implant diseases as compared to healthy controls
Sorsa *et al*., 2020(113)	Investigate the effectiveness of aMMP8 PoC mouthwash in diagnosing peri-implantitis	Healthy subjects (n = 20) Peri-implantitis (n = 20)	Mouth rinse samples	aMMP8 Lateral flow immunoassay test (ImplantSafe®)	Peri-implantitis, diagnosed clinically and radiographically	aMMP8 PoC test correctly diagnosed all healthy and Peri-implantitis cases
Lähteenmäki *et al*., 2020(114)	Assessing the accuracy aMMP-8 PISF POC test (ImplantSafe) as compared to other biomarkers of peri-implantitis. Evaluating the value of aMMP-8 lateral-flow PoC technologies in non-invasively monitoring periodontal treatment outcomes	Patients with peri-implantitis (n = 26) Healthy control (n = 26) Periodontitis patients (n = 15)	PISF, mouth rinse samples	aMMP8 Lateral flow immunoassay test (ImplantSafe®), (PerioSafe®)	Peri-implantitis, diagnosed by presence of PPD ≥4mm, BOP, radiographic bone loss ≥2 mm, PI, FI, mobility index Self-reported oral health (SROH)-questionnaires	aMMP8 PoC test discriminated health from peri-implantitis with higher accuracy than BOP, PMN-elastase, MMP9, TIMP1, and myeloperoxidase SROH can be used as adjunctive diagnostic method but not as alternative for oral fluid biomarkers

Through the research carried out during the second article, it was identified that recently, two PoC chairside test kits have been developed - PerioSafe® PRO DRS (dentognostics GmbH, Jena) and ImplantSafe® DR (dentognostics GmbH, Jena) - to identify the presence of active MMP-8 on the saliva samples. The kits are like a COVID test or a pregnancy test, providing two lines of results indicating a higher risk of periodontitis/peri-implantitis (figure 6). The advantages of these tests are that they are inexpensive, noninvasive, do not require specialized equipment or trained staff and provide a quick result with high sensitivity and specificity (97).

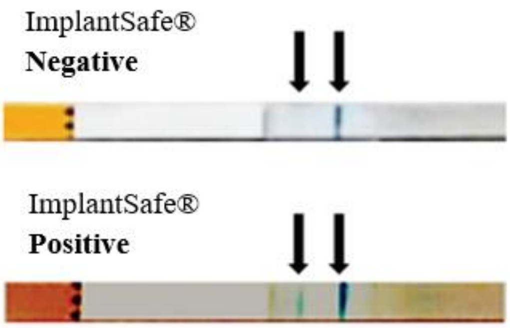

Figure 6: ImplantSafe kit (negative: < 20 ng/ml; positive: > 20 ng/ml), a site-specific peri-implant sulcular and gingival crevicular fluid (PISF/GCF) (aMMP)-8 point-of-care test (adapted from Sorsa et al. (2021) (93)).

Once the presence of active MMP-8 has been identified in the sample, a quantitative analysis can be performed using the PerioSafe® PRO DRS (dentognostics GmbH, Jena) and ImplantSafe® DR (dentognostics GmbH, Jena) ORALyser, which is already a commercially available quantitative reader-based on aMMP-8 oral fluid specific point-of-care/chair-side lateralflow reader-equipped immunotests (92). The results can be both qualitative and quantitative use the ORALyser reader (92,114–117) (figure 7).

Figure 7: ImplantSafe® DR (dentognostics GmbH, Jena) and ORALyser reader(118).

The tests have diagnostic sensitivity and specificity 76–90% and 96%, respectively, corresponding to an odds ratio of > 72 (93,119). The test results are quantitatively available by the reader in 5 min PoC/chair-side. The tests have been shown to be useful to screen susceptible sites and patients, differentiate active and inactive peri-implantitis sites, predict the future disease progression, and monitor the treatment.

The PerioSafe® PRO DRS (dentognostics GmbH, Jena) and ImplantSafe® DR (dentognostics GmbH, Jena) aMMP-8-PoC test kits are efficient tools in improving the accuracy of diagnostic and prognostic of periodontal or peri-implant diseases and they are commercially available and approved technologies by the FDA on the United States of America and European Union (88,115,120). They are widely used in Europe as can be seen in Figure 8, however, they have not yet been implemented in the Iberian Peninsula.

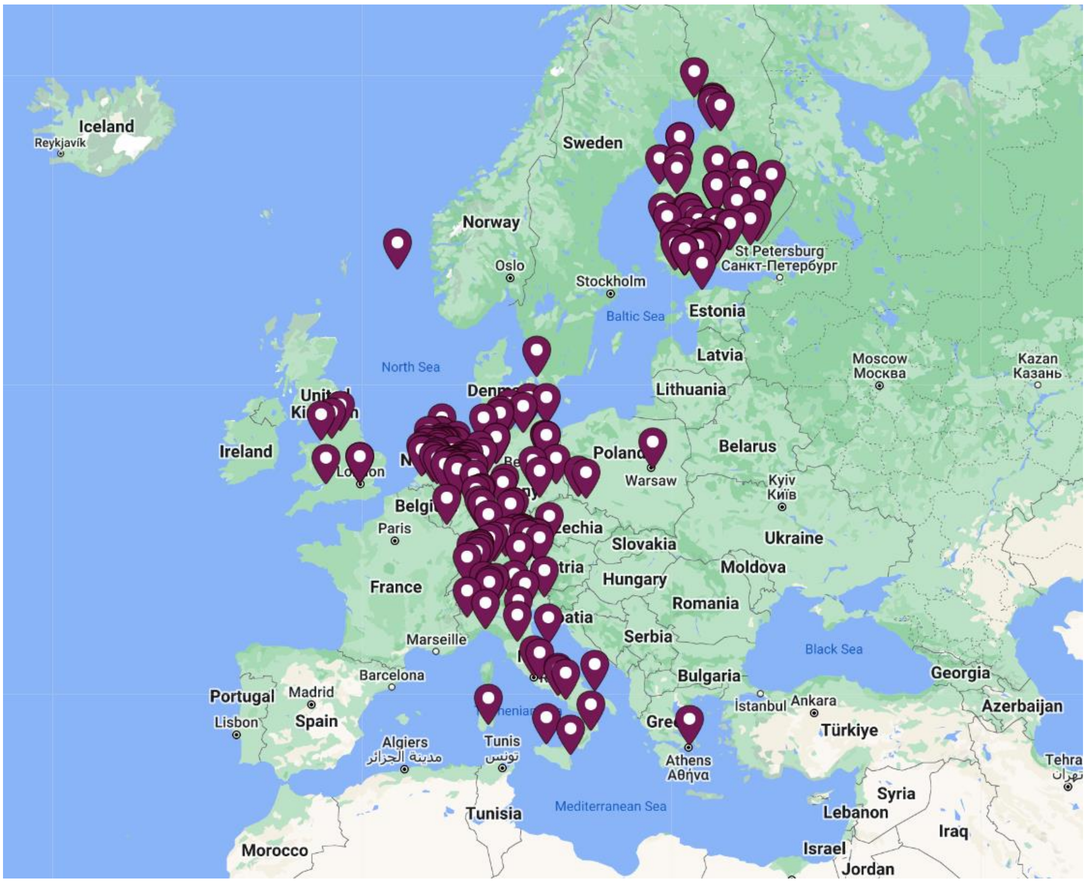

Figure 8: Distribution of European clinics that adopt clinical protocols for maintaining periodontal or peri-implant health using PerioSafe® and ImplantSafe®(118).

PerioSafe® PRO DRS (dentognostics GmbH, Jena) and ImplantSafe® DR (dentognostics GmbH, Jena) and ORALyzer® tests have already been validated to function with a single biomarker, such as, aMMP-8 that is demonstrated as a biomarker of significance in the new classifications of both periodontitis and peri-implantitis. It is available as a mouthrinse (PerioSafe®PRO DRS (dentognostics GmbH, Jena)) and sulcular fluid/gingival crevicular fluid (ImplantSafe®DR (dentognostics GmbH, Jena)) variants(92,97,113,117). The difference between both tests is that PerioSafe®PRO DRS (dentognostics GmbH, Jena) indicate the general periodontal status, whereas the ImplantSafe®DR (dentognostics GmbH, Jena) variant can be used as a site-specific test. Both have the advantage of being an easy-to-use tool-kit, and the possibility that either the patients themselves or general clinicians could interpret the result and understand whether or not they should refer the patient to a dentist.

The ImplantSafe®DR (dentognostics GmbH, Jena) /ORALyzer® test kits, already used clinically, can be a helpful adjunct tool in enhancing the diagnosis and prognosis of peri-implantar diseases.

5.3 PERCEPTION AND CLINICAL USABILITY OF A RISK ASSESSMENT TOOL

In a further step, a risk assessment tool was selected, and a protocol was defined to test its usability, as well as the perception of dentists regarding the implementation of a risk tool in current clinical protocols. The tool chosen was the Implant Disease Risk Assessment (IDRA) for several reasons: because it is recent, because of its visual way of presenting the factors and the score, because it is quick to complete and, mainly, because the authors allow incorporation of changes in line with future developments or additional factors become evident from the literature modifications.

This tool is used with the purpose of minimizing the chance of developing peri-implant tissue breakdown. By understanding the key factors associated with the development of peri-implant diseases documented in the literature the clinician may selectively address such factors to improve the outcomes for implant therapy (121). The analyses of results from recent studies addressing risk factors/indicators for biological complications associated with dental implants have identified eight important factors that may contribute to the development of peri-implantitis:

1) history of periodontitis;
2) percentage of sites with bleeding on probing (BOP);
3) prevalence of probing depth ≥ 5 mm;
4) bone loss in relation to the patient's age;

5) periodontitis susceptibility(121);

6) supportive periodontal therapy;

7) implant restorative depth;

8) prosthesis-related factors.

These eight parameters have been combined in an octagon that helps visualizing the risk for disease development (figure 9).

A comprehensive evaluation using this functional diagram will provide an individual total risk profile and determine the need for measures targeting risk reduction. This tool was designed for assessing risk for an individual patient after implant therapy. However, IDRA may be useful as a checklist to identify modifiable risks prior to implant therapy and as a tool for the clinician to communicate the level of risk to the patient.

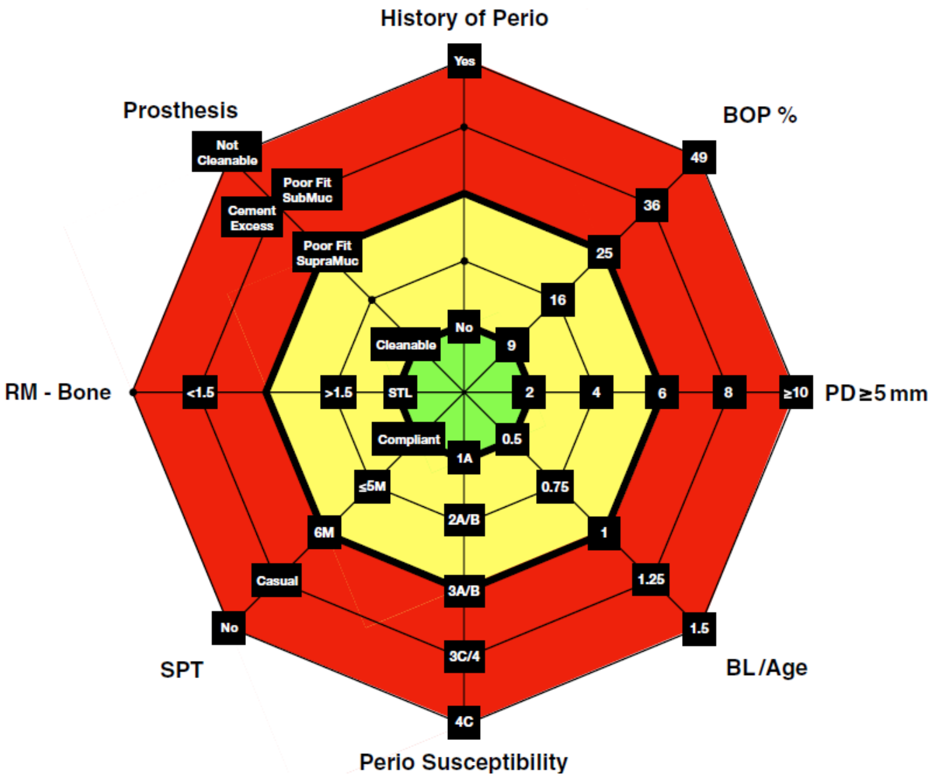

Figure 9: Functional diagram of IDRA tool (121).

After carrying out the usability test, it was concluded that participants shared favorable beliefs and expectations about IDRA Tool and its ability to increase the early detection and prevention of peri-implant diseases. Although the participants evaluated the tool as good, assigning it a usability value of 77.2 on the System Usability Scale (SUS) scale (Figure 10), some suggestions were pointed out that will be analyzed in order to understand the feasibility of being incorporated in the proposed tool that I propose to create in this doctoral thesis(122).

Figure 10: System Usability Scale (SUS)(123).

According to the study population, clinicians dedicated to the field of Implantology, four additional modifications should be considered:

1) considering the relation between contour angle and peri-implant tissue height;
2) automatic periodontal classification in the IDRA tool after completing the periodontogram in the clinical software;
3) presentation of a flow chart to assist therapeutic decisions alongside the final score defined by the IDRA tool;
4) integrating of precision tests.

In fact, the topic “Distance from the Restorative margin (RM) of the implant-supported prosthesis to the bone” was the second that raised the most doubts when filling out the tool. One suggestion was to modify this factor by the height of the prosthetic abutment; however, this factor has been updated over the years, with the supracrestal complex continuing to be of great importance in predicting peri-implant risk. However, currently, greater importance is attributed to the contour angle, soft tissue dimensions, and the thickness of the mucosa have been shown to be important parameters for health and stability. Currently, the abutment height is a variable dependent on the contour angle (124).

The initial concepts of the peri-implant mucosa height were influenced by concepts first described in the periodontium, from the "Biologic Width" (125) to the recently introduced "Supracrestal Tissue Attachment" (7,126). Terms such as "Peri-Implant Soft Tissue Barrier" (127), "Peri-implant Mucosa" (128), and "Peri-implant Phenotype" (129) have been utilized to describe the peri-implant tissues. These studies have advocated the importance of an essential minimum height of the peri-implant mucosa to ensure the stability of the soft tissue and marginal bone in the long term. This essential height, which has previously corresponded to the concept of the "Biologic width," has been approximated to be between 2.5 and 4 mm in human studies(127,130,131). Failure to secure this soft tissue height has been associated with marginal bone loss recession, and other soft tissue complications (132,133).

The recently introduced concept of the Implant Supracrestal Complex suggested that the dimensions and morphology of the peri-implant mucosa are interrelated with the design of the prosthesis, from which it cannot be studied in isolation. Understanding these interrelations, as well as the clinical implications of the 1) design of the prosthesis, 2) the transmucosal components, and 3) implant position can help devise effective implant treatments and reduce the risk of complications in the long term (134).

Puisys *et al.*(124) affirm the "contour" of the transmucosal components of the implant is what determines the transition from the narrow and cylindrical implant platform to the wider and rectangular or oval-shaped cervical margin of the crown. For this transition to be smooth and gradual, an adequate vertical height is required; otherwise, the contour will present a steep transition with wide contour angles. This transition can be approached with a simple trapezoid rectangle. Some studies (135–137) have suggested that overcontouring of the prosthesis more than 30° is correlated with an increased risk for peri-implantitis in bone-level implants. In other hand, the convexity of the prosthesis profile has been correlated with increased recession (138) , marginal bone loss (139), and when combined with overcontouring, peri-implantitis.

Considering a clinical situation, in the case of a posterior implant prosthesis, the implant supracrestal complex represents a transition from a commonly 4 mm wide implant platform to a cervical margin with an approximate width of 8 mm at the buccal/lingual. If the angle of the contour is to be 30°, the Pythagoras theorem and trigonometry can be utilized to calculate the corresponding essential height (Figure 11). Figure 11b shows the reducing of the height to 2 mm, resulting in a drastic increase of the contour angle to 45°(124).

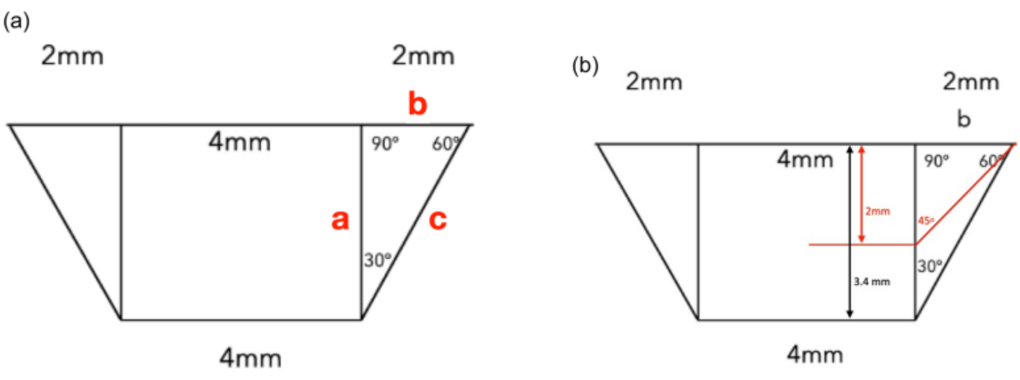

Figure 11: Application of the Pythagorean theorem in the trapezoid approximation of the Implant Supracrestal (Adapted from Puisys et al.(124)).

This concept is in line with what was proposed by clinicians during the usability test, as it is possible with only 3 measurements (implant diameter, buccal/lingual and interproximal distance) to determine if the angle and consequently the height of the abutment are adequate for a smooth and gradual transition between the implant and the prosthesis. Ideally, in the not-too-distant future, it will be possible to take these measurements with artificial intelligence algorithms and, automatically, determine whether the abutment height obeys contour angle 30º.

Regarding the second topic (automatic periodontal classification in the IDRA tool after completing the periodontogram in the clinical software), this suggestion was mentioned by most of the participants, since the new classification is more complex and becomes a limitation when completing the questionnaire. Therefore, they suggest integrating the tool with the clinical software, and at the end of completing the periogram, the respective diagram's vector would automatically be filled.

Regarding the third suggestion (presentation of a flow chart to assist therapeutic decisions alongside the final score), some clinicians suggested that parallel to the presentation of the score, it should be shown a flow chart/decision-tree to assist clinicians' decisions. This decision tree has already been created by the International Team for implantology, where the author of IDRA was part of the team (figure 12).

This type of diagrams is very useful as it makes clinical protocols standardized and, on the other hand, also allows, from a pedagogical point of view, to systematize the strategies to be adopted in cases of peri-implant disease

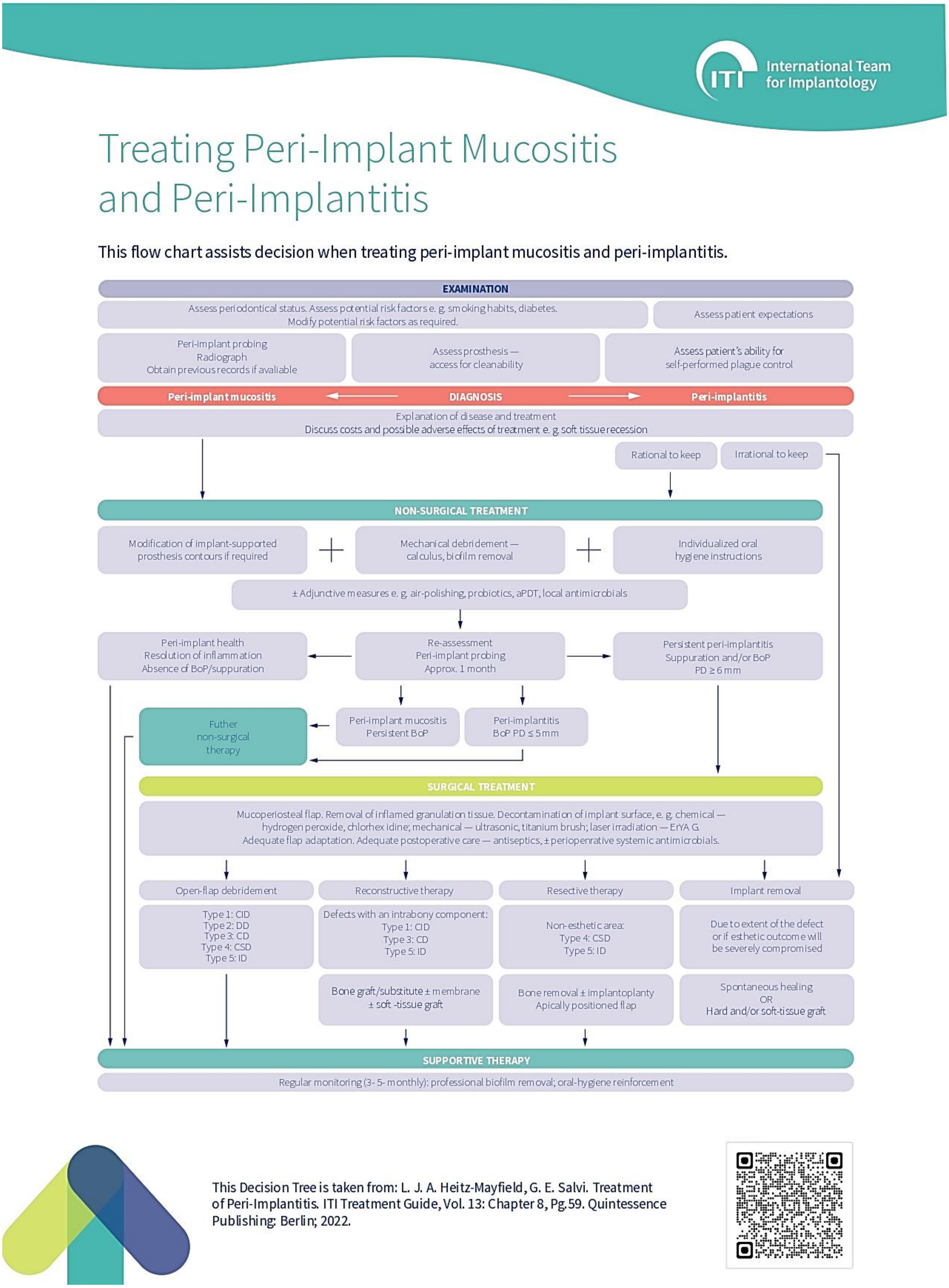

Figure 12: A decision tree for treating peri-implant mucositis and peri-implantitis

5.4 PROPOSAL OF A DENTAL FAILURE PREDICTION TOOL (IFPT)

Based on these findings presented so far, it is possible to create a proposal tool that will integrate the assumptions of precision medicine, incorporating updated strategies to support the diagnosis and predict the dental implant success. This proposal tool can be seen as an eventual update to IDRA, since it was mentioned by the authors that as “additional factors become evident from the literature modifications of the diagram may be appropriate”(121).

The proposed tool created is called the Implant Failure Prediction Tool – IFPT. The IFPT is not yet translated into digital format, it only exists as a concept design. The logo was already created by the communication department of FMDUCP (figure 13).

Figure 13: Implant Failure Prediction Tool – IFPT Logo.

Figure 14 shows the IFPT tool, combining eight selected risk factors for dental implant failure. Each vector has its own scale for risk profiles.

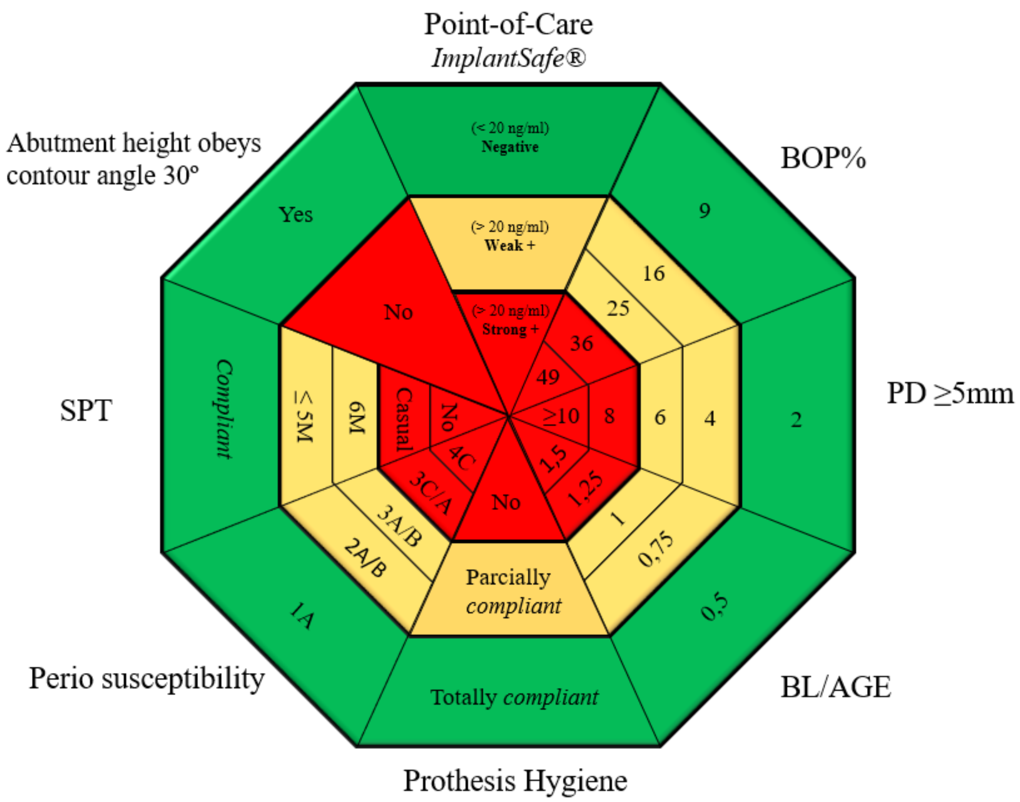

Figure 14: IFPT Tool - Each vector represents one risk parameter categorized according to data found in the literature.

As it can be seen, six factors are common to the IDRA, with an agglutination of the "History of periodontitis" vector with the "periodontitis susceptibility" vector. This junction is justified by the fact that we want to integrate the IFPT with clinical software, and it is of interest that all the information capable of periodontally classifying the individual is gathered in the same vector. Of the eight factors presented in the IFPT, six are common to the IDRA, which are presented in detail below.

5.4.1 Percentage of sites with BOP

Bleeding on gentle probing represents an objective inflammatory parameter, which has been incorporated into known index systems, for the evaluation of periodontal (140) and peri-implant conditions(141). Percentage of sites with BOP may also be used as an individual assessment parameter representing the host response to the bacterial challenge. The incorporation of the BOP% into the PRA established a BOP prevalence of 25% as a cutoff point between patients who maintained periodontal stability for 4 years and patients with recurrent disease in the same time frame (142,143). Further evidence of BOP % (ranging between 20%–30%) determining a higher risk for periodontal disease progression was demonstrated in a number of studies (143,144). Bleeding on probing at implant sites was also shown to be associated with disease progression (145–147). The percentage of BOP is, therefore, used as a second risk indicator in the IDRA functional diagram. The scale runs in a quadratic mode of 9, 16, 25, 36, and >49% being the critical values on the vector. This assessment encompasses the BOP% for all tooth and implant sites. Individuals with low BOP % (<10%) may be regarded as patients with a low risk for disease development, while patients with BOP% >25% should be considered to be at higher risk for tissue breakdown(148).

5.4.2 Prevalence of probing depths ≥5 mm

High numbers of deep periodontal pockets (PD ≥ 5 mm) and deepening of pockets during SPT has been associated with high risk of periodontal disease progression (144). It has also been shown that putative periodontal pathogens from deep residual pockets at teeth may colonize implant sites(141).

Furthermore, the presence of higher numbers of residual pockets was associated with peri-implantitis development in the medium (149)to long-term (150). In assessing the patient's risk for peri-implant disease development, the number of tooth and implant sites with a PD ≥ 5 mm is assessed as the third risk indicator in the IDRA functional diagram. The scale runs in a linear mode with 2, 4, 6, 8, ≥10 being the critical values on this vector. Individuals with one or two pockets with a PD ≥ 5 mm may be regarded as patients at low risk, while patients with more than six sites with PD ≥ 5 mm are regarded as individuals at high risk for development of biological complications.

5.4.3 Periodontal bone loss in relation to age

The extent and prevalence of periodontal attachment loss as evaluated by the height of alveolar bone on radiographs may represent the most obvious indicator of subject risk for periodontal disease progression when related to the patient's age(151). Periodontal bone loss has been identified as a risk factor for the development of peri-implant disease in two large randomly selected population studies (152,153). Therefore, the extent of alveolar bone loss in relation to the patient's age is estimated as the fourth risk indicator for disease development in the functional IDRA diagram. The estimation of the loss of alveolar bone is performed in either periapical radiographs in which the worst tooth site affected is grossly estimated in % of the root length or on bitewing radiographs in which the worst site affected is estimated in mm. On bitewing radiographs, 1 mm is considered to be equal to 10% bone loss. The percentage is then divided by the patients age resulting in a factor. As an example, a 40-year-old patient with 20% of bone loss at the worst affected site would score BL/age = 0.5. Another 40-year-old patient with 50% bone loss at the worst affected site would score BL/age = 1.5. The scale runs in increments of 0.25 of the factor BL/age with 0.5 being the critical value to discriminate between low and moderate risk and 1.0 being the value for moderate and high risk. This, in turn, means that a patient who has lost a higher percentage of the alveolar bone than his/her age is at high risk regarding this vector in a multifactorial assessment.

5.4.4 Periodontitis susceptibility

In 2017, the World Workshop on Classification of Periodontal and Peri-implant diseases proposed a new system for the classification of periodontal diseases encompassing extent, severity and complexity in a staging modality(154). In addition, the progression rate and hence the susceptibility to disease was incorporated with a grading modality(154). It, therefore, seems logical to add the staging and grading for periodontal disease as a vector influencing disease development and progression for peri-implant diseases. According to the IDRA (Figure 1), only Stage 1 Grade A represents low risk. Stage 2 represents moderate (from the middle node in the moderate range) or higher risk. Stage 3 represents moderate (from the outer node in the moderate range) or higher risk. Stage 4 represents high risk. Regarding grading: Grade B represents moderate (from the middle node in the moderate range) or higher risk and Grade C represents high risk. The number of teeth that have been lost due to periodontitis is incorporated in the staging of the 2017 classification. As the evidence for an association with peri-implantitis remains equivocal regarding cigarette smoking and diabetes mellitus, these modifying factors are considered as potential risk indicators or emerging risk factors (155). Therefore, they are not represented in the IDRA by individual vectors; instead, they are incorporated within the grading of the 2017 classification of periodontal diseases. This classification assigns a non-smoker to Grade A (slow rate of progression), a smoker <10 cigarettes per day is Grade B (moderate rate of progression) and a smoker ≥ 10 cigarettes per day represents Grade C (high risk of progression). A patient with no diagnosis of diabetes is assigned as Grade A (slow rate of progression). A patient with diabetes and HbA1c $< 7.0\%$ is Grade B (moderate rate of progression) and HbA1c $\geq 7.0\%$ is Grade C (rapid rate of progression).

5.4.5 Supportive periodontal therapy (SPT)

There is strong evidence that a regular recall system rendering appropriate supportive care is of utmost importance for peri-implant health and stability (156–158). Therefore, the sixth vector of the IDRA deals with the compliance of patients and supportive care rendered by the clinician. Obviously, no supportive care represents a high risk for peri-implant disease development while full compliance with a recommended and calculated maintenance care interval results in low risk for disease development. A systematic review determined that a recall interval of less than or equal to 5 months, on average may represent a time frame compatible with maintenance of peri-implant health(158).

5.4.6 Prosthetic hygiene

Although this parameter is common to IDRA, it is necessary to direct this evaluation to a less subjective and more personalized indicator. In this sense, patient *compliance* was evaluated in this vector. Since even with the best intentions and efforts by health professionals, the expected goals will not be achieved if patients do not have a certain degree of *compliance*.

In this sense, the goal is to measure the plaque index at each visit by means of a plaque developer and then fill in the corresponding vector. The main goal is besides recording concrete data capable of quantitatively identifying the bacterial plaque of that individual, it also works as an awareness and form of doctor-patient communication in the improvement of oral health care.

5.4.7 Point-of-Care/Chair-side tests

IFPT incorporate a PoC test - ImplantSafe® test kit- a helpful adjunct tool in enhancing diagnosis and prognosis of peri-implant diseases. aMMP8 levels exceeding 60 ng/mL potentially predict poor prognosis of peri-implantitis to periodontal treatment. In figure 15, is represented a cut-off points of aMMP8 have been determined for a healthy state (<6.46 ng/mL), gingivitis/peri-mucositis (6.64–20 ng/mL), periodontitis/peri-implantitis that respond favorably to the treatment (20–60 ng/mL), and progressive periodontitis that does not respond to the treatment (>60 ng/mL) (92,159). The latter two conditions could respond favorably to periodontal therapy which is reflected by downregulation of aMMP8 expression in oral fluids (black continuous line) or the destruction of periodontal tissues further progress if neglected (orange continuous line).

This test uses PISF, so it must be performed by a professional before any clinical intervention, the whole procedure must be carried out according to the manufacturer's guidelines. Briefly, the PISF strip of the test kit was placed apically into the peri-implant sulcus for 30 seconds, after which the strip was placed in the vial containing 0.6 ml of elution buffer for 5 minutes. Afterward, a dipstick from the test kit was dipped into the elution fluid for 15 seconds and then removed, ready for analysis with the ORALyzer® reader (Dentognostics GmbH). Five minutes later, the quantitative result was noted from the result window of the reader. The qualitative result was visible as blue lines on the dipstick; a single blue line indicating an aMMP-8 level less than 20 ng/ml (negative); and two blue lines as aMMP-8 level more than 20 ng/ml (positive). The visible result on the dipstick was documented with a photograph too. Among the positive cases with two lines there existed both weak or thin(ner) (a weak positive) or strong or thick(er) (a strong positive) second line (93).

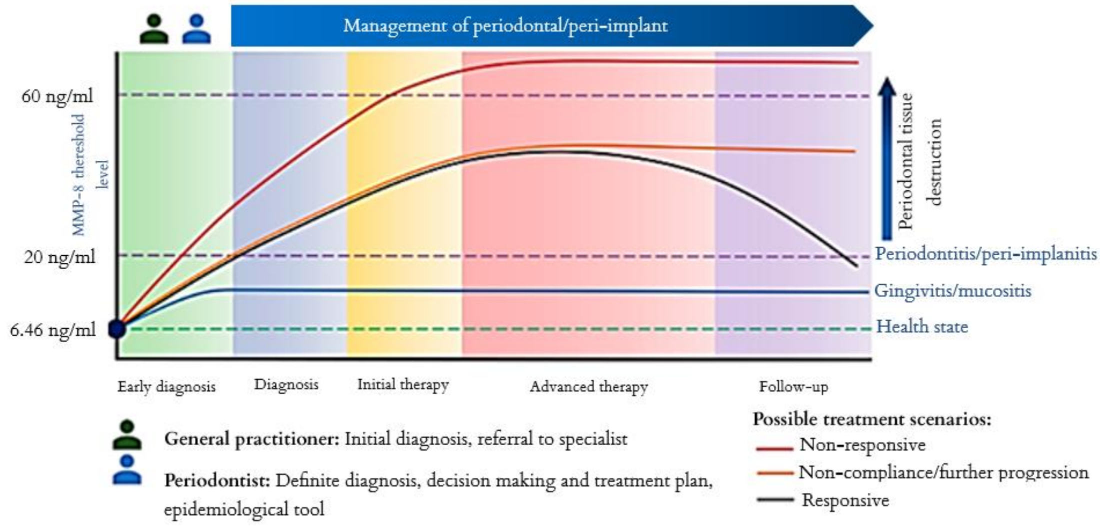

Figure 15: Cut off point of aMMP8 to differentiate periodontal/peri-implant health and disease (adapted from Sorsa et al.(88)).

5.5 IFPT – A PREDICTIVE TOOL

Based on the assumptions of precision medicine, as already addressed in this doctoral thesis, it is necessary to start collecting data of different levels of complexity, from the most superficial such as medical history, to the most complex, such as *omics* data - deep phenotyping. In this sense, IFPT will be used, in parallel, in two different ways:

- At present, assist in the early diagnosis of peri-implant diseases, namely mucositis and peri-implantitis (figure 16), through ImplantSafe® test kits.

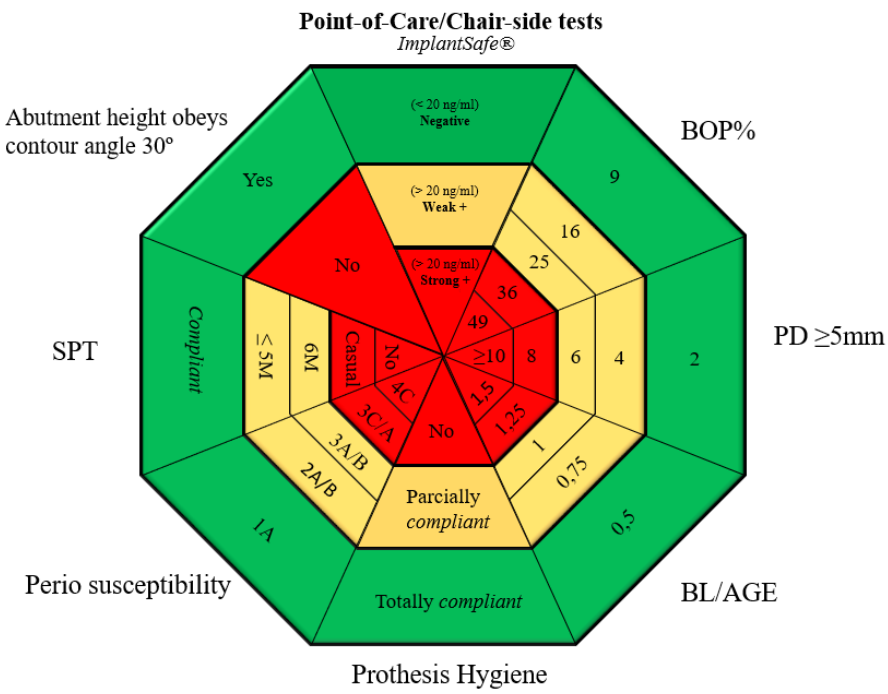

Figure 16: IFPT Tool possible to use today to aid in the early diagnosis of peri-implant diseases.

1) In the foreseeable future, it will function as an individualized tool that will accurately predict the success of the dental implant (figure 17).

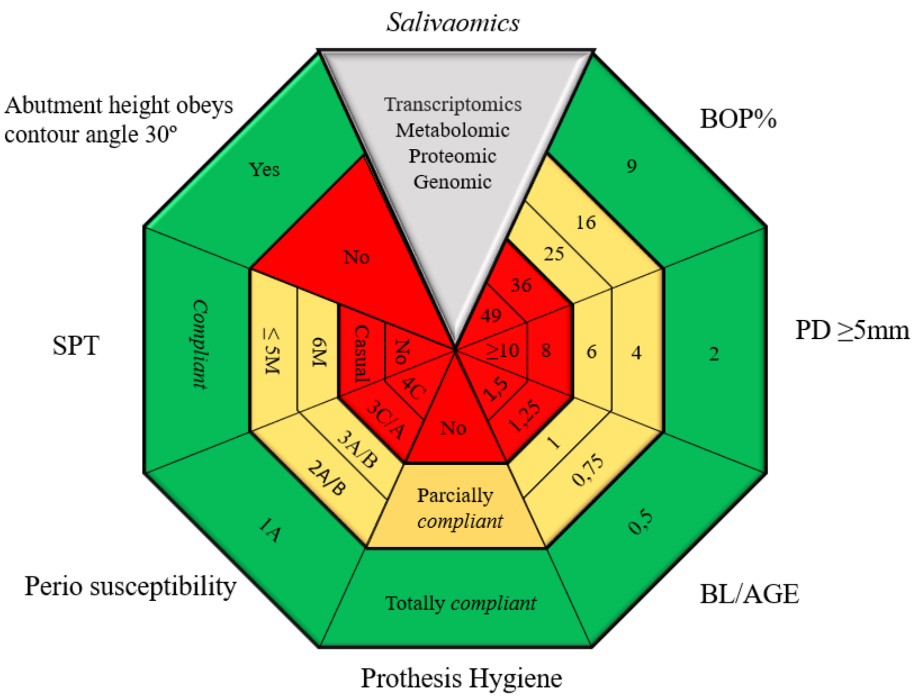

Figure 17: IFPT Tool capable of long-term prediction of dental implant success and accurate prognosis.

Currently, this tool has all the conditions to be used according to the assumptions of the first aim topic. Its completion and risk calculation follows the same rationale of IDRA. However, to improve the doctor-patient communication and to make it easier for the patient to understand and follow up his/her own case, the result provided by the IFPT is given as traffic signal, besides the written indication of the risk of developing a peri-implant disease. Thus, from the patient's point of view, the greenish the diagram is, the more possibility of implant success patient has. If a yellow vector appears, it means that the patient should modulate his or her behavior to change it to the green level; the more reds appear in the diagram, the higher the risk of developing peri-implant disease.

The calculation of the individual risk of developing peri-implant disease was based on the IDRA tool. Consequently, a low-risk patient (figure 18) has all parameters in the low-risk categories or at the most one parameter in any the moderate-risk category except in the PoC/ chair-side vector. A moderate-risk patient (figure 19) has at least two parameters in the moderate-risk category but at most one parameter in the high-risk category except in the PoC/ chair-side vector. A high-risk patient (figure 20) has at least two parameters in any the high-risk category.

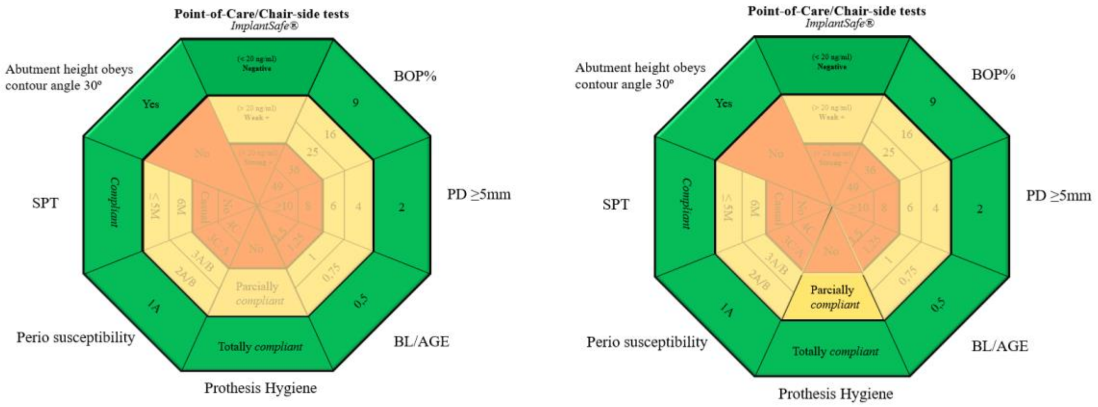

Figure 18: IFPT Low-risk category.

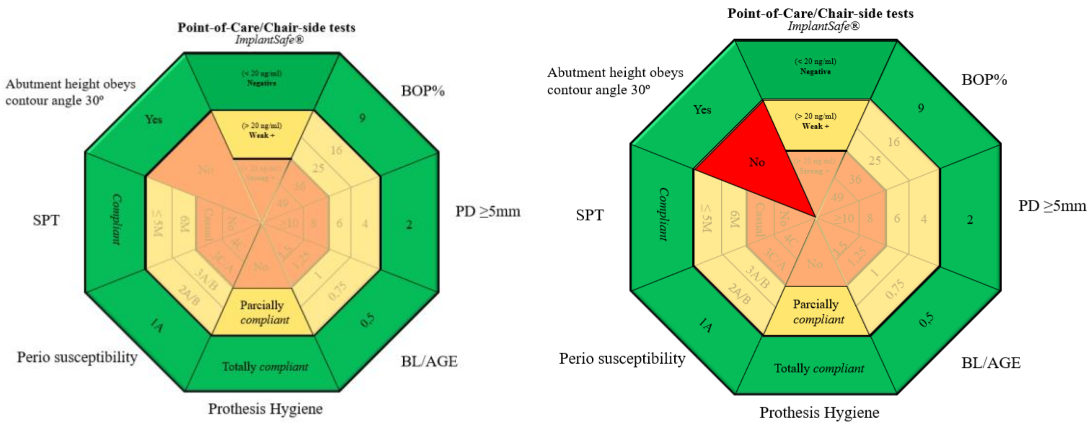

Figure 19: IFPT Moderate-risk category.

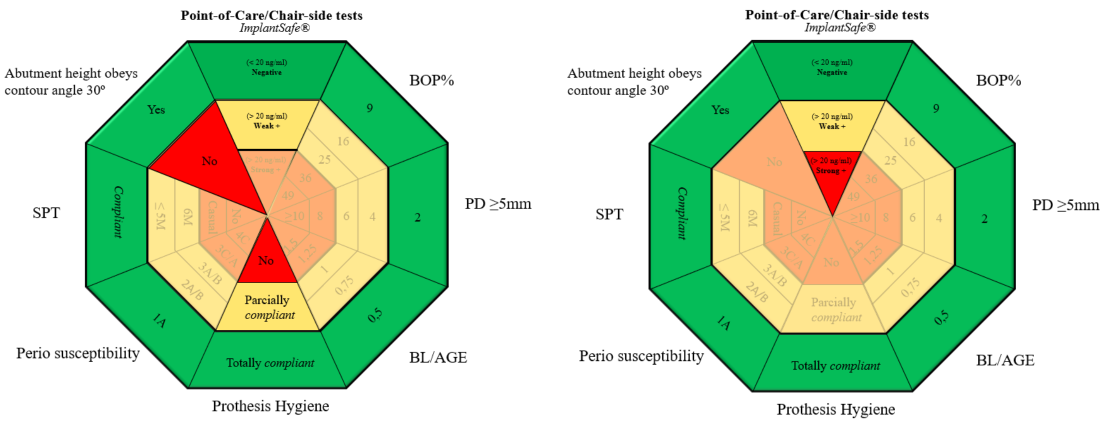

Figure 20: IFPT High-risk category.

On the other hand, our second objective with IFPT is to create a tool capable of predicting prognoses in the foreseeable future. Currently, what is within our reach is to start creating a diagnostic and prognostic model. Defining a longitudinal study methodology that allows the loading of as many clinical cases as possible into the IFPT ("inputs") and, through the follow-up of these patients, to identify/diagnose possible clinical outcomes of peri-implantitis, mucositis or peri-implant health ("outcomes") over time (Figure 21). In this way, as the data are processed by means of IA algorithms, the variables/predictors with more significance for the determination of the implant failure may be identified and, at the same time, their respective weights in the predicting algorithm. This methodology will be detailed throughout the next topic of the discussion. This tool will use AI algorithms, namely artificial neural networks technology, allowing the tool to accumulate different functions as it is used. Artificial neural networks are highly flexible models and have been used in medicine to explore relationships between various physiological variables and to build predictive models (160). In this way it is possible to define an algorithm capable of indicating with accuracy and precision treatment response.

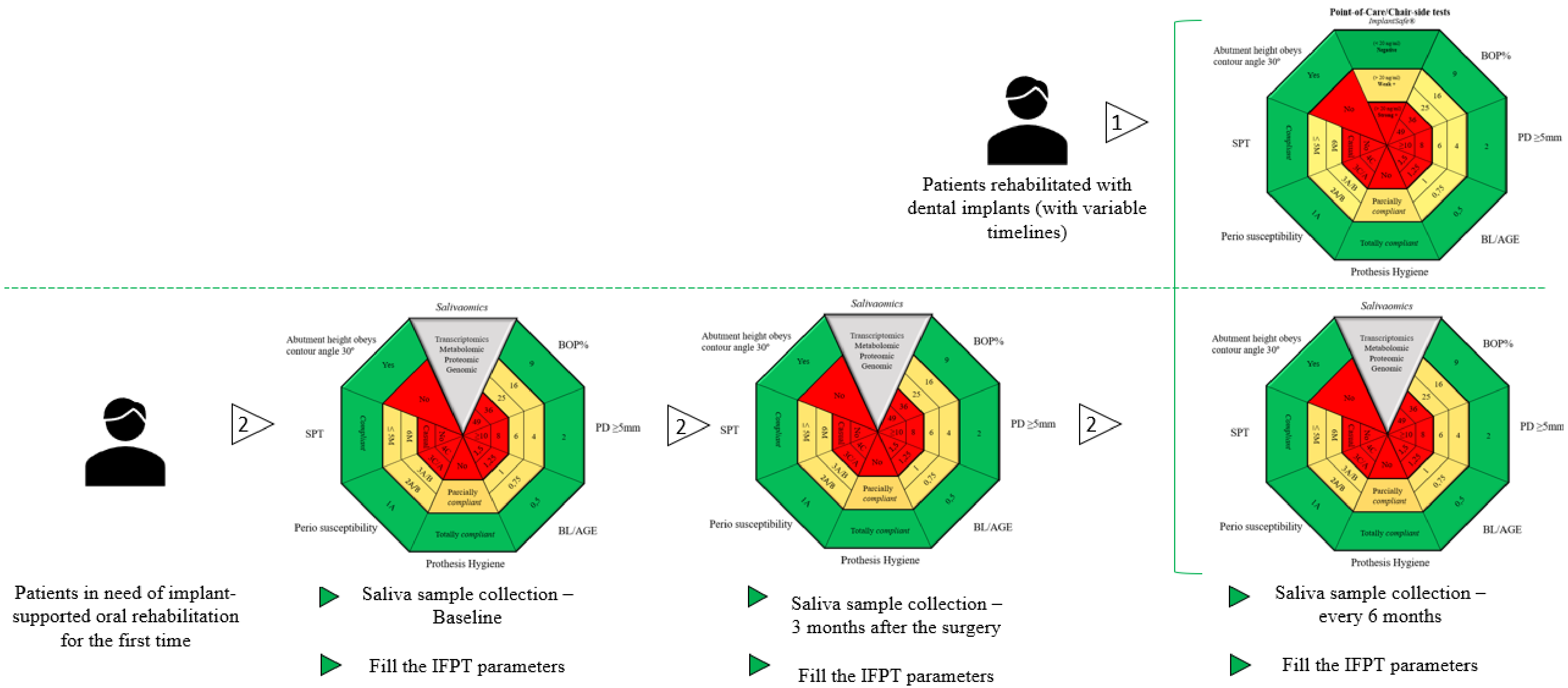

Figure 21: Longitudinal study methodology. The number 1 corresponds to a first aim of IFPT, and the number 2 corresponds to the second aim topic, which represents a longitudinal study to start putting into practice the assumptions of precision dentistry.

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5.5.1 IFPT – a predictive tool for dental implant prognosis

To answer point two and questions such as "Can I predict if a certain patient will develop peri-implantitis?" or "How is it possible that two patients with identical clinical conditions, one presents peri-implantitis and the other does not?" or like the ones in figure 22 it is necessary to develop a longitudinal study methodology involved in a lengthy process - precision medicine framework.

How do I explain to this healthy patient that the implant did not osseointegrate?

Will I be successful in the rehabilitation of this polymedicated patient?

How do I know the implant will osseointegrate?

Patient compliance 100%, peri-implantitis in all implants, how is this possible?

Figure 22: Examples of questions.

The concept incorporates the following ideas:

1) as the process includes a number of feedback loops, there is no steady endpoint of precision medicine where, finally, precise medical care is provided to the patients;
2) the cycle implies that there are ongoing efforts to become ever more precise;
3) finer and more accurate stratifications of patients can be interim results of the overall process, which is captured by the term “stratified medicine”. An important aspect of this framework therefore is that data assessed in the patients are used to try to develop clinically relevant models, and that the results of these analyses then inform the further assessment of patients, thus emphasising the definition of a process and precision medicine as an evolving result.

As a starting point, data are gathered on different levels of complexity, from medical history to omics data through specific proteomic or genomic analyses of a biological fluid, for example saliva. To these data inputs it is necessary to associate outcomes, at different moments of assessment, waiting for the different disease outcomes to occur, which is the justification for the delay in this type of process. In the case of peri-implant diseases, it would have to take at least 4 years to have a peri-implantitis outcome. The more repeated cycles of patient evaluation, data collection, data processing and model building yield patient groups higher resolution the models has. In the first cycles, patients are categorized into diagnostic and/or prognostic groups based on few obvious characteristics (Physical examination, lifestyle, medical history); later cycles define more specific strata of patients using more in-depth data (Immunology/histology and omics); final cycles may eventually target individual patients with specific data profiles (figure 23).

Based on these results, the methodology of the longitudinal study underway at FMDUCP described above (figure 21) has the capacity to answer complex questions that can only be unraveled through deep phenotyping strategies.

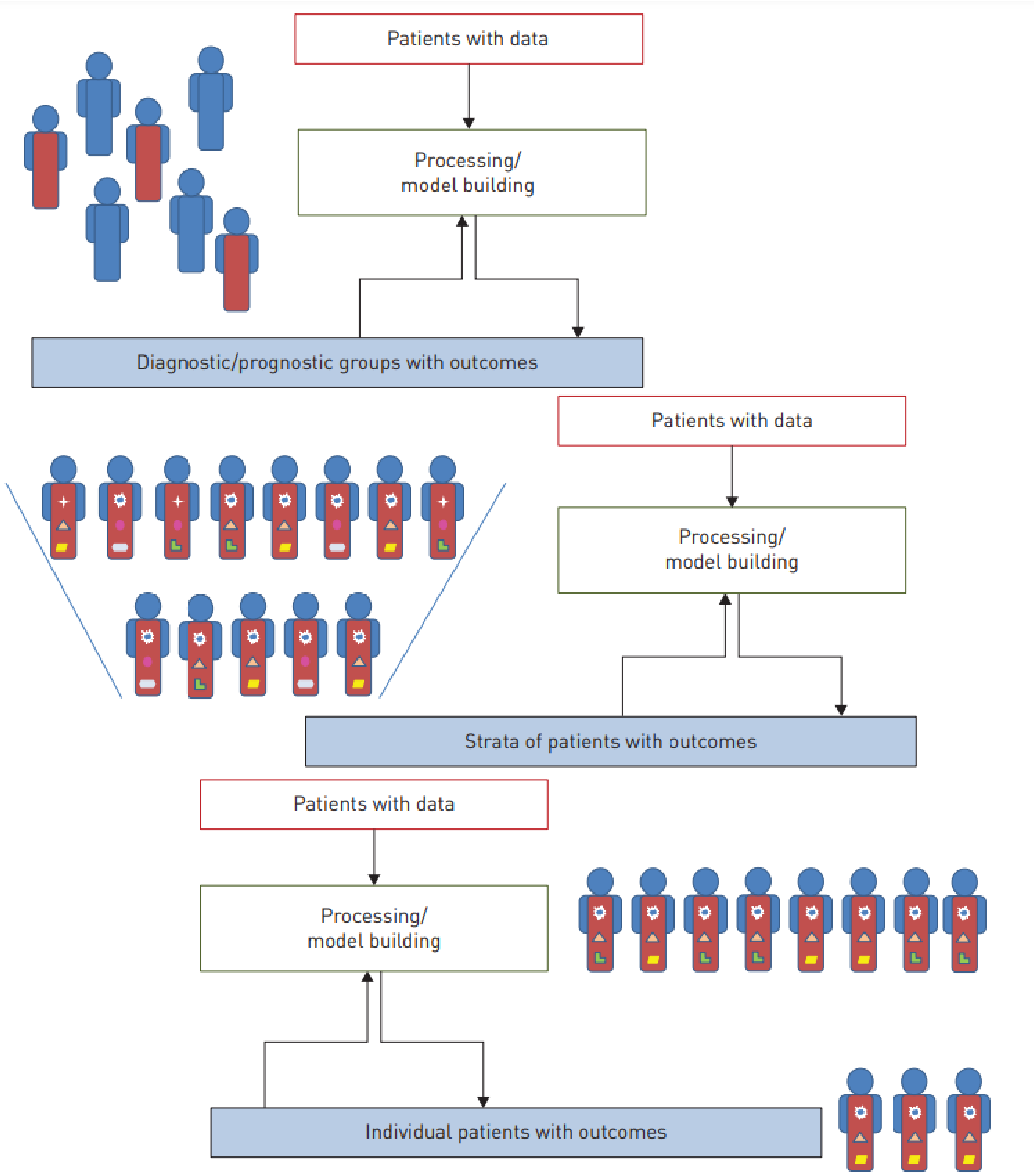

Figure 23: Repeating cycles evolving precision medicine (adapted from Konig et al.(45)).

This research, in a first phase, analyzed how artificial intelligence and omics are applied in the field of implantology as a tool to assist in the planning and diagnosis of peri-implant diseases. It was concluded that currently there are already well-defined clinical protocols based on AI algorithms, however, the same is not true for omics. Although it is demonstrated in the literature that the combination of both strategies in clinical protocols allows clinical precision approach, since it reduces misdiagnosis and, eventually, allows the prediction of possible outcomes, there are still no protocols in this sense.

In this sense, chair-side diagnostic devices currently available in the market that, during follow-up visits in parallel with conventional diagnostic methods, could support the clinical decision in the detection of peri-implant diseases were searched. The ImplantSafe®DR (dentognostics GmbH, Jena) /ORALyzer® test kits, already used clinically, could be a helpful adjunct tool in enhancing the diagnosis and prognosis of peri-implant diseases.

Therefore, recognizing the diagnostic potential of bioinformatics strategies, it became necessary to understand the acceptance of risk assessment tools for the development of peri-implantitis by the community of dentists dedicated to implantology. Among other conclusions drawn from this study, the characteristics that the tool that I proposed to create would have to follow were identified.

Based on these findings, a proposal for a peri-implant risk prediction tool - IFPT - was created. This tool brings together factors widely known and used by clinicians during intraoral assessment, as well as chair-side testing or proteomic analysis through salivary collection. Currently, the IFPT is incorporated in a clinical protocol with 2 paths: 1) At present, assist in the early diagnosis of peri-implant diseases, namely mucositis and peri-implantitis, through ImplantSafe® test kits; 2) in the foreseeable future, it will function as an individualized tool that will accurately predict the success of the dental implant.

The IFPT is currently being implemented in the usual clinical protocols used in the implant supported oral rehabilitation appointments at the university clinic of the FMDUCP.

6 CONCLUSIONS

This research concluded that well-defined clinical protocols based on AI algorithms already exist for the planning and diagnosis of peri-implant diseases (ImplantSafe®DR (dentognostics GmbH, Jena) /ORALyzer® test kits are currently available on the market). However, this is not the case for omics methodologies.

The created peri-implant risk prediction tool: IFPT brings together factors widely known and used by clinicians during intraoral assessment, as well as in-office tests or proteomic analysis through saliva collection. This tool supports the early diagnosis of peri-implant diseases, namely mucositis and peri-implantitis, through ImplantSafe® test kits. It is foreseeable that in the near future, it can function as an individualised tool for predicting dental implant success.

7 CONCLUSIONES

Esta investigación concluyó que actualmente ya existen protocolos clínicos bien definidos basados en algoritmos de IA para la planificación y diagnóstico de enfermedades periimplantarias (Actualmente están disponibles en el mercado los kits de prueba ImplantSafe®DR (dentognostics GmbH, Jena) /ORALyzer®,). Sin embargo, no ocurre lo mismo con las metodologías ómicas.

La herramienta creada de predicción del riesgo periimplantario: IFPT reúne factores ampliamente conocidos y utilizados por los clínicos durante la evaluación intraoral, así como las pruebas realizadas en la consulta o el análisis proteómico a través de la recogida de saliva. Esta herramienta ayuda al diagnóstico precoz de las enfermedades periimplantarias, concretamente la mucositis y la periimplantitis, a través de los kits de prueba ImplantSafe®. Es previsible que en un futuro próximo, pueda funcionar como una herramienta individualizada para predecir el éxito del implante dental.

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9 APPENDICES

9.1 APPENDIX I. ORIGINAL ARTICLES QUALITY RATINGS (JCR 2022)

PAPER 1

Bornes RS, Montero J, Correia ARM, Rosa NRDN. Use of bioinformatic strategies as a predictive tool in implant-supported oral rehabilitation: A scoping review. J Prosthet Dent. 2023 Feb;129(2): 322.e1-322.e8.
ISSN: 0022-3913
Impact Factor: 4.148 JCR Science Edition: 2022.
Category: Oral Surgery
Position in the category: 6/49 (T1/Q1).

PAPER 2

Bornes R, Montero J, Correia A, Marques T, Rosa N. Peri-implant diseases diagnosis, prognosis and dental implant monitoring: a narrative review of novel strategies and clinical impact. BMC Oral Health. 2023 Mar 30;23(1):183.
ISSN: 1472-6831
Impact Factor: 3.747 JCR Science Edition: 2022.
Category: Dentistry (miscellaneous)
Position in the category: 36/109 (T1/Q1).

PAPER 3

Bornes R, Montero J, Ferreira A, Rosa N, Correia A. Dentists' perceptions and usability testing of the Implant Disease Risk Assessment IDRA, a tool for preventing peri-implant disease: a qualitative study. Journal of Dentistry. 2023;104630.
ISSN: 0300-5712
Impact Factor: 1.189 JCR Science Edition: 2022.
Category: Dentistry (miscellaneous)
Position in the category: Q1

9.2 APPENDIX II. TESIS RESUMIDA EN CASTELLANO

9.2.1 Introducción

Uno de los objetivos más desafiantes en el campo de la rehabilitación oral es el tratamiento de pacientes parcial y totalmente edéntulos en términos de función y estética. A pesar del motivo que pueda haber causado la pérdida de dientes, la rehabilitación oral dental o implantosoportada debe planificarse siempre en función de su previsibilidad y duración. Teniendo en cuenta el crecimiento de la población y la esperanza media de vida, actualmente hay muchas más personas que buscan tratamientos y soluciones para los dientes que han perdido, lo que en última instancia se traduce en una mayor demanda de tratamientos de regeneración ósea, así como de implantes dentales (1,2).

A pesar de los muchos avances recientes en implantología, el éxito de la rehabilitación oral implantosoportada sigue siendo un reto. El fracaso de los implantes puede deberse a diversos factores, como la periimplantitis, la osteointegración inadecuada, la técnica quirúrgica, las afecciones sistémicas y la selección del paciente. Una de las complicaciones dentales más temidas es la periimplantitis, que implica una pérdida de tejido óseo periimplantario debida a la invasión bacteriana de los tejidos periimplantarios como resultado de un desequilibrio entre la cantidad/calidad bacteriana y las capacidades defensivas del huésped (4).

El desarrollo de herramientas que integren los factores de riesgo asociados al fracaso es crucial para mejorar las tasas de éxito de los implantes. Estas herramientas permiten a los clínicos evaluar el riesgo de fracaso, tomar decisiones informadas, personalizar los planes de tratamiento y aplicar medidas preventivas. En última instancia, contribuyen a mejorar el éxito general y los resultados a largo plazo de la rehabilitación oral con implantes.

La fase de mantenimiento en implantología es clave para el éxito del tratamiento y debe ser un objetivo en la planificación de los casos para obtener unas condiciones óptimas que promuevan medidas higiénicas por parte del paciente y del profesional. Debido a la complejidad derivada de la naturaleza multifactorial de la rehabilitación implantosoportada, el desarrollo de metodologías capaces de integrar todos los factores/predictores sólo es posible con el uso de herramientas informáticas. En los últimos años, ya se han realizado algunas aproximaciones en este sentido, mediante las cuales algoritmos de inteligencia artificial (IA) pueden apoyar el diagnóstico o identificar implantes dentales a través de imágenes radiográficas. Estas estrategias apoyan el pronóstico del implante, prediciendo eventuales condiciones clínicas como pérdida ósea temprana, mucositis o periimplantitis (35,36). Además, al utilizar métodos basados en redes neuronales avanzadas - machine learning - es posible prever la complejidad y el riesgo potencial durante el proceso de rehabilitación de implantes dentales (37,38).

Todas las evidencias científicas, así como las herramientas de evaluación utilizadas hoy en día por los profesionales, se basan estrictamente en parámetros clínicos, analíticos y radiográficos que, de hecho, proporcionarán al médico algunas directrices terapéuticas limitadas para hacer frente a la complejidad multifactorial de los procedimientos de rehabilitación implantosoportada. Además, desde el punto de vista del diagnóstico y estadiaje de las enfermedades periimplantarias, existen métodos que sólo pueden registrar el estado preexistente y no la propia condición actual, no considerando el cuadro clínico del paciente. Además, no contempla las condiciones sistémicas, el estilo de vida, los cambios hormonales y el envejecimiento, entre otros aspectos, relacionados con los procesos inflamatorios individuales que, en consecuencia, pueden influir en la respuesta inmunológica local, ya sea alrededor de una zona dentaria (periodontitis), o alrededor de una zona de implantes dentales (periimplantitis).

Teniendo en cuenta todos estos hechos y reconociendo la complejidad multifactorial de la enfermedad inflamatoria oral, la necesidad de proporcionar análisis precisos basados en un protocolo clínico estándar requiere diagnósticos respaldados por tecnologías ómicas, como la proteómica. La ómica tiene como objetivo la caracterización y cuantificación colectiva de moléculas biológicas que se traducen en la estructura, dinámica y función de un organismo. Las tecnologías ómicas han emergido como una poderosa herramienta para investigar diferentes mecanismos moleculares entre los estados de salud y enfermedad, descubriendo moléculas (Biomarcadores) comúnmente utilizadas en medicina para determinar objetivamente el estado de la enfermedad o las respuestas a una intervención terapéutica y que pueden ser dianas de nuevas terapias (41,42).

Esta metodología es la clave para la introducción de la medicina de precisión en odontología, principalmente en el campo de la rehabilitación oral, ya que puede adaptar el procedimiento a seguir teniendo en cuenta las características biológicas, sociales (económicas y educativas) y de estilo de vida del paciente. A pesar de ello, puede actuar con prudencia frente a las patologías que puedan producirse y su progresión en fases tempranas. Para dar un diagnóstico creíble y un plan de tratamiento específico, respetando las necesidades de cada paciente, han surgido múltiples investigaciones en muy diversos campos de la salud, centrándose en la genómica, la proteómica y la metabolómica. El concepto de medicina de precisión no significa necesariamente la creación de dispositivos médicos exclusivos para un paciente, sino la capacidad de clasificar a los miembros individuales en subpoblaciones que difieren en su susceptibilidad a una enfermedad o tratamiento específicos. El objetivo principal es reducir los errores de diagnóstico, desarrollar resultados y evitar efectos colaterales innecesarios, aclarando la razón por la que tal individuo puede desarrollar un cuadro clínico de periimplantitis, en comparación con otros con las mismas condiciones que no desarrollaron el mismo estado (41,43).

Es reconocida la importancia de los biomarcadores como metodología a implementar en odontología, especialmente en áreas donde la variabilidad interindividual presenta una gran relevancia, como durante los mecanismos biológicos asociados a la osteointegración y en los procesos de fracaso tardío de los implantes dentales (mucositis o periimplantitis).

Teniendo en cuenta el objetivo y la transversalidad de la medicina de precisión, es imperativo crear protocolos que pretendan dar respuesta a sus supuestos, idealmente mediante la aplicación de algoritmos de IA y metodologías ómicas como los biomarcadores. Esta tesis doctoral pretende dar los primeros pasos hacia la creación de un protocolo a seguir en casos de rehabilitación oral implantosoportada, que cumpla con los supuestos de la medicina de precisión.

9.2.2 Objectivos y Justificación

La medicina de precisión es un enfoque relativamente nuevo e innovador que comienza a implementarse en odontología, habiendo dado un paso importante con la implementación de biomarcadores en la nueva clasificación de periodoncia y condiciones periimplantarias.

Varios campos de la odontología pueden aprovechar esta metodología, sin embargo, el que más destaca es la rehabilitación oral implantosoportada debido a la etiología multifactorial del fracaso del implante, como el fracaso de la osteointegración, la mucositis o la periimplantitis. Actualmente se conocen numerosos factores asociados a estas condiciones clínicas, así como los protocolos utilizados en el diagnóstico y tratamiento de estas patologías. Sin embargo, esta metodología solo es capaz de identificar la patología cuando ya está instalada, y no antes de que haya daño tisular. Es necesario introducir estrategias bioinformáticas, combinando inteligencia artificial y ciencias ómicas, en protocolos clínicos convencionales ampliamente utilizados y conocidos por los odontólogos, aumentando la precisión de la detección temprana de enfermedades periimplantarias y periodontales, la predicción de la progresión de la enfermedad y el seguimiento de los efectos del tratamiento.

Los objetivos específicos de este estudio fueron:

1. Revisar la literatura sobre bioinformática (inteligencia artificial y ciencias ómicas), abordando el estado del arte de cómo se ha utilizado para predecir el éxito de los implantes dentales.

2. Revisar cómo las pruebas moleculares en el punto de atención (PoC) actualmente disponibles pueden ayudar en la detección temprana de enfermedades periimplantarias.

3. Identificar un kit de prueba comercialmente disponible y aprobado en la Unión Europea que ya haya sido validado para funcionar con biomarcadores de periimplantitis y que use fluido oral para diagnosticar.

4. Investigar la percepción de los dentistas sobre la implementación de una herramienta para apoyar la evaluación del riesgo periimplantario.

5. Crear una prueba de utilidad para identificar las mejoras que se pueden realizar en la herramienta IDRA.

6. Crear una herramienta experimental para predecir el éxito de los implantes dentales.

9.2.3 Articulos Originales

Bornes RS, Montero J, Correia ARM, Rosa NRDN. Use of bioinformatic strategies as a predictive tool in implant-supported oral rehabilitation: A scoping review. J Prosthet Dent. 2023 Feb;129(2): 322.e1-322.e8.

<u>Resumen</u>

<u>Planteamiento del problema.</u> El uso de estrategias bioinformáticas está creciendo en los protocolos de implantes dentales. La expansión actual de las ciencias ómicas y los algoritmos de inteligencia artificial (IA) en aplicaciones implantes dentales no ha sido documentada y analizada como herramienta predictiva para el éxito de los implantes dentales.

<u>Objetivo.</u> El propósito de esta revisión de alcance era analizar cómo los algoritmos de inteligencia artificial algoritmos de inteligencia artificial y las tecnologías ómicas en el campo de la implantologia éxito de los implantes dentales.

<u>Material y métodos.</u> Se utilizó la lista de verificación Preferred Reporting Items for Systematic Reviews and Meta-Analyses para revisiones de alcance. Se creó una estrategia de búsqueda en PubMed y Web of Science para responder a la pregunta "How is bioinformatics being applied in the area of implantología oral como herramienta predictiva del éxito de los implantes"?

<u>Resultados.</u> Se incluyeron 13 artículos en esta revisión. Sólo 3 aplicaban modelos bioinformáticos combinando algoritmos de IA y tecnologías ómicas. Estos estudios destacaron 2 puntos clave para la creación de la medicina de precisión: el fenotipado poblacional profundo y la integración de las ciencias Omics en los protocolos clínicos. La mayoría de los estudios identificados aplicaban la IA únicamente en la identificación

la identificación y clasificación de sistemas de implantes, la cuantificación de la pérdida ósea periimplantaria y el análisis óseo tridimensional para planificar la colocación de implantes. análisis ósseo tridimensional, planificando la colocación de implantes.

Conclusiones. Los criterios convencionales utilizados actualmente como técnica de diagnóstico y seguimiento de los implantes dentales son insuficientes y tienen baja precisión. Los modelos que aplican IA algoritmos de IA combinados con metodologías de precisióndbiomarcadores son extremadamente útiles en la creación de la medicina de precisión, permitiendo a los odontólogos pronosticar el éxito del implante. Se necesitan herramientas que integren los distintos tipos de datos, incluidos los de imagen, moleculares, factores de riesgo y de riesgo y las características del implante, para predecir el éxito de los implantes de forma más precisa y personalizada.

Bornes R, Montero J, Correia A, Marques T, Rosa N. Peri-implant diseases diagnosis, prognosis and dental implant monitoring: a narrative review of novel strategies and clinical impact. BMC Oral Health. 2023 Mar 30;23(1):183.

Resumen

Antecedentes: El diagnóstico periimplantario y periodontal se basa principalmente en un conjunto de medidas clínicas y en la evaluación de imágenes radiográficas. Sin embargo, estos parámetros clínicos por sí solos no son suficientes para determinar, y mucho menos predecir, la pérdida ósea periimplantaria o el futuro fracaso del implante. El diagnóstico precoz de las enfermedades periimplantarias y su ritmo de avance puede ser posible mediante la evaluación de biomarcadores. Una vez identificados, los biomarcadores de la destrucción de los tejidos periimplantarios y periodontales pueden alertar a los clínicos antes de que se produzca el fracaso clínico. Por lo tanto, es importante considerar el desarrollo de pruebas diagnósticas con especificidad para un biomarcador concreto, que indiquen la actividad actual de la enfermedad.

Métodos: Se creó una estrategia de búsqueda en Pubmed y Web of Science para responder a la pregunta: "¿Cómo pueden las pruebas moleculares actualmente disponibles pueden ayudar a la detección precoz de enfermedades periimplantarias y arrojar luz sobre mejoras en los dispositivos de diagnóstico en el punto de atención".

Resultados: Los kits de prueba PerioSafe® PRO DRS (dentognostics GmbH, Jena) e ImplantSafe® DR (dentognostics GmbH, Jena ORALyzer®), que ya se utilizan clínicamente, pueden ser una herramienta complementaria útil para mejorar el diagnóstico y el pronóstico de las enfermedades periodontales y periimplantarias. Gracias a los avances de la tecnología de sensores, los biosensores pueden realizar a diário de los implantes dentales o las enfermedades periodontales, contribuyendo a la atención sanitaria personal y mejorando el actual status quo de la gestión sanitaria y la salud humana.

Conclusiones: Basándose en los hallazgos, se hace más hincapié en el papel de los biomarcadores en el diagnóstico y seguimiento de las enfermedades periodontales y periimplantarias. Combinando estas estrategias con los protocolos tradicionales, los profesionales podrían aumentar la precisión de la detección precoz de las enfermedades periodontales y periimplantarias, la predicción de la progresión de la enfermedad y el seguimiento de los resultados del tratamiento.

Palabras clave: Enfermedades periimplantarias, Biomarcadores, Diagnóstico molecular, Pronóstico, Medicina dental de precisión, *Point-of-care test*

Bornes R, Montero J, Ferreira A, Rosa N, Correia A. Dentists' perceptions and usability testing of the Implant Disease Risk Assessment IDRA, a tool for preventing peri-implant disease: a qualitative study. Journal of Dentistry. 2023;104630.

Resumen

Introducción: el objetivo era explorar las percepciones de los odontólogos respecto a la aplicación de una herramienta informática de evaluación del riesgo de que un paciente desarrolle periimplantitis

Materiales y métodos: se presentó la Herramienta de Evaluación del Riesgo de Enfermedad de los Implantes (IDRA) a una muestra de conveniencia de siete dentistas que trabajaban en una clínica universitaria, a los que se pidió que utilizaran IDRA con la información de tres casos clínicos mientras pensaban en voz alta y luego rellenaban la Escala de Usabilidad del Sistema (SUS). Se utilizó una técnica de entrevista semiestructurada con grabación de audio para permitir la libre expresión de las percepciones de los participantes relacionadas con el IDRA. La información de las entrevistas fue categorizada y analizada por los autores.

Resultados: hasta donde sabemos, este es el primer estudio realizado para desarrollar una prueba de utilidad del IDRA, evaluando la eficacia, eficiencia y satisfacción de los usuarios. Hubo más variaciones en las respuestas cuanto mayor era el grado de complejidad del caso clínico. En general, los participantes clasificaron la herramienta como buena, obteniendo valores de utilidad de 77,2 (DE 19,8) y de aprendizaje de 73,2 (DE 24,5).

Conclusión: deben tenerse en cuenta cuatro factores adicionales para mejorar la herramienta IDRA: 1) considerar la relación entre el ángulo de contorno y la altura del tejido periimplantario; 2) clasificación periodontal automática en la herramienta IDRA tras completar el periodontograma en el software clínico; 3) presentación de un diagrama de flujo que ayude a tomar decisiones terapéuticas junto con la puntuación final definida por la herramienta IDRA; 4) integración de pruebas de precisión como Implantsafe® DR (dentognostics gmbh, Jena) y Oralyzer®(dentognostics gmbh, Jena).

Importancia clínica: la etiología y patogénesis de las enfermedades periimplantarias es multifactorial. Estas herramientas deben seguir una integración natural para poder aplicarse fácilmente en un entorno clínico. Es importante estudiar su utilidad desde el punto de vista de los clínicos, evaluando la eficacia, la eficiencia y la satisfacción de los usuarios.

Palabras clave: enfermedad periimplantaria; pronóstico; toma de decisiones; informática dental; utilidad; Piénsalo en voz alta.

9.2.4 Discusión

Nuestra revisión bibliográfica sobre el uso de estrategias bioinformáticas como herramienta predictiva en la rehabilitación oral implantosoportada indicó su aplicabilidad en varios dominios. El ejemplo de cómo las ciencias ómicas pueden implementarse en protocolos clínicos para el mantenimiento de implantes dentales para ayudar en el diagnóstico precoz de enfermedades periimplantarias y cómo diferentes algoritmos de inteligencia artificial, como las redes neuronales convencionales, el aprendizaje profundo y, el aprendizaje automático pueden ayudar en la creación de herramientas de apoyo a la toma de decisiones clínicas.

Todas estas aplicaciones son especialmente relevantes en esta época, en que cada vez se destaca más el papel de la inteligencia artificial como apoyo a las actividades cotidianas. En este sentido, según nuestra revisión bibliográfica, es seguro que se producirá un crecimiento exponencial de herramientas que integren este tipo de estrategias capaces de soportar diversas decisiones clínicas.

La mayoría de los artículos seleccionados están relacionados con la planificación y el mantenimiento de la salud periimplantaria. Estas dos fases de la rehabilitación oral son las más relevantes para el éxito clínico y las que más apoyo bioinformático deberían tener. El éxito de la rehabilitación presupone una planificación adecuada, así como un seguimiento apropiado, con el objetivo de detectar precozmente cualquier complicación técnica o biológica.

De acuerdo con los datos analizados, la mayoría de los estudios estaban relacionados con la identificación del sistema de implantes dentales a través de radiografías 2D. Sin embargo, los autores reconocen estas dos dimensiones como una limitación y apuntan para futuros estudios el uso de imágenes tridimensionales, mientras que otros estudios ya están diseñando algoritmos para el análisis de imágenes tridimensionales[29, 74-78]. Sin embargo, también se están creando algoritmos para identificar la pérdida de hueso marginal y el éxito de la osteointegración del implante, basándose en la presencia de factores de riesgo del paciente [75, 79, 80]. Estos avances permiten que los diagnósticos clínicos sean más rigurosos, ya que no dependen de la subjetividad inherente a los protocolos clínicos convencionales, sino de algoritmos de IA precisos. Tanto los modelos convencionales como los de IA sólo pueden reconocer una patología periimplantaria cuando ya está instalada, evaluando la gravedad de la patología mediante mediciones. ¿Es posible diagnosticar estas afecciones antes de que se instalen? ¿Es posible predecir con exactitud el pronóstico periimplantario? Estas son algunas de las preguntas que se plantean, y que hacen imperativa la creación de una metodología que obedezca a los presupuestos de la medicina de precisión.

El punto de partida de este proceso es el fenotipado profundo de los individuos. Esta fase consiste en recopilar datos individuales de los pacientes a distintos niveles, desde los datos más simples a los más complejos. Por lo tanto, deben recopilarse datos relativos a la historia clínica, el estilo de vida, los exámenes físicos, las pruebas de laboratorio básicas, las imágenes radiográficas y los datos obtenidos mediante las ciencias ómicas (figura 4). En la actualidad, las ciencias ómicas, especialmente la genómica y la proteómica, han despertado interés en la comunidad científica, ya que permiten identificar diferencias moleculares entre individuos, que pueden explicar muchas de las variaciones clínicas. Permitiendo responder a preguntas como: ¿Cómo es posible que pacientes con iguales condiciones clínicas, unos desarrollen periimplantitis y otros no?

Por lo tanto, es crucial implementar pruebas moleculares en el *Point-of-care* (PoC) en los nuevos protocolos clínicos, concretamente en aquellos utilizados durante las citas de seguimiento.

Posteriormente, se realizó una segunda revisión para identificar y analizar cómo los *Point-of-care* actualmente disponibles pueden ayudar en la detección precoz de enfermedades periimplantarias, identificando qué PoC podrían incorporarse a esta nueva metodología clínica para la evaluación del riesgo periimplantario.

La tecnología Point-of-Care pretende evaluar los niveles de biomarcadores que han demostrado estar asociados al estado de la enfermedad. Estas pruebas ya se han utilizado en medicina general para los biomarcadores de coagulación sanguínea, inmunológicos y cardiovasculares. Además, algunas de estas pruebas, como las pruebas de embarazo y para los niveles de glucosa en sangre, están disponibles para uso doméstico[81].

Entre las moléculas, las enzimas (MMP8 en particular) se han examinado principalmente y se han traducido como pruebas *chair-side*. Por lo general, estas pruebas no se utilizan mucho en la clínica debido a la complejidad del procedimiento y a su baja sensibilidad y especificidad [83], mientras que los kits de pruebas de PoC desarrollados más recentemente pueden proporcionar resultados en 5-7 minutos, con alta sensibilidad y especificidad [85, 86].

El nivel de MMP8, en particular, se incrementó notablemente en proporción a la gravedad de la enfermedad, lo que potencialmente permite medir y reflejar con precisión el estado clínico pasado, actual y previsto[89, 90]. Recientemente, se ha revisado de forma exhaustiva la eficacia de las pruebas PoC/*chair-side* utilizando saliva, GCF, PISF y enjuague bucal[91].

Las zonas periimplantarias patológicamente implicadas mostraron un patrón similar de nivel elevado de MMP8 en el PISF al observado en las zonas con periodontitis [97-99], con una fuente celular similar derivada principalmente de células inflamatorias, en particular PMN (figura 5)[99]. Se observó que la mayor gravedad de la pérdida ósea y la actividad osteolítica durante la periimplantitis estaban asociadas con el nivel de aMMP-8 en los PISF[99], lo que confirmó otro estudio[100]. Los resultados de un análisis retrospectivo de 10 años mostraron una correlación positiva entre la expresión aumentada de MMP8 en el GCF y el PISF y el grado de inflamación[96]. Al igual que en la dentición natural, la respuesta de los tejidos que soportan los implantes dentales al tratamiento puede predecirse midiendo los niveles de aMMP-8 en los fluidos orales [93].

De hecho, la introducción de una prueba en el punto de atención basada en la MMP8 que utilice la saliva como plataforma para las pruebas de evaluación periodontal es un "cambio de juego" que no sólo proporciona datos sobre la situación actual, sino que también identifica individualidades susceptibles y predice el éxito del tratamiento [88, 90, 106].

A través de la investigación llevada a cabo durante el segundo artículo, se identificó que recientemente se han desarrollado dos kits de pruebas de evaluación de la situación en el consultorio - PerioSafe® PRO DRS (dentognostics GmbH, Jena) e ImplantSafe® DR (dentognostics GmbH, Jena) - para identificar la presencia de MMP-8 activa en las muestras de saliva. Los kits son como una prueba COVID o una prueba de embarazo, y proporcionan dos líneas de resultados que indican un mayor riesgo de periodontitis/periimplantitis (figura 6). Las ventajas de estas pruebas son que son baratas, no invasivas, no requieren equipos especializados ni personal formado y proporcionan un resultado rápido con una alta sensibilidad y especificidade, 76,5% y el 96,7%, respectivamente [85, 86, 91].

Estas pruebas permiten detectar la presencia de caries, predecir la progresión futura de la enfermedad y supervisar el tratamiento.

Los kits de prueba aMMP-8-PoC PerioSafe® PRO DRS (dentognostics GmbH, Jena) e ImplantSafe® DR (dentognostics GmbH, Jena) son herramientas eficaces para mejorar la precisión del diagnóstico y el pronóstico de las enfermedades periodontales o periimplantarias, y están disponibles comercialmente y son tecnologías aprobadas por la FDA en los Estados Unidos de América y la Unión Europea [82, 109, 114]. Su uso está muy extendido en Europa como se puede observar en la Figura 8, sin embargo, aún no se han implantado en la Península Ibérica.

Las pruebas PerioSafe® PRO DRS (dentognostics GmbH, Jena) e ImplantSafe® DR (dentognostics GmbH, Jena) y ORA¬Lyzer® ya han sido validadas para funcionar con un único biomarcador - aMMP-8 - que se demuestra como un biomarcador de importancia en las nuevas clasificaciones tanto de periodontitis como de periimplantitis.

En un paso posterior, se seleccionó una herramienta de evaluación del riesgo y se definió un protocolo para probar su utilidade, así como la percepción de los odontólogos respecto a la implementación de una herramienta de riesgo en los protocolos clínicos actuales. La herramienta elegida fue la Implant Disease Risk Assessment (IDRA) por varias razones: porque es reciente, por su forma visual de presentar los factores y la puntuación, porque es rápida de completar y, principalmente, porque los autores permiten incorporar cambios en función de futuros desarrollos o de factores adicionales que se pongan de manifiesto a partir de las modificaciones de la literatura.

Esta herramienta se utiliza con el fin de minimizar la posibilidad de que se produzca una descomposición del tejido periimplantario. Al conocer los factores clave asociados al desarrollo de enfermedades periimplantarias documentadas en la literatura, el clínico puede abordar selectivamente dichos factores para mejorar los resultados del tratamiento con implantes [115]. Los análisis de los resultados de estudios recientes que abordan los factores/indicadores de riesgo de complicaciones biológicas asociadas a los implantes dentales han identificado ocho factores importantes que pueden contribuir al desarrollo de periimplantitis:

1) antecedentes de periodontitis
2) porcentaje de zonas con sangrado al sondaje (BOP)
3) prevalencia de profundidad de sondaje ≥ 5 mm;
4) pérdida ósea en relación con la edad del paciente;
5) susceptibilidad a la periodontitis [115];
6) terapia periodontal de apoyo;
7) profundidad de restauración del implante;
8) factores relacionados con la prótesis.

Estos ocho parámetros se han combinado en un octógono que ayuda a visualizar el riesgo de desarrollo de la enfermedad (figura 9).

Una evaluación exhaustiva utilizando este diagrama funcional proporcionará un perfil de riesgo total individual y determinará la necesidad de medidas dirigidas a la reducción del riesgo. Esta herramienta se diseñó para evaluar el riesgo de un paciente individual tras un tratamiento con implantes.

Tras realizar la prueba de utilidade, se concluyó que los participantes compartían creencias y expectativas favorables sobre IDRA Tool y su capacidad para aumentar la detección precoz y la prevención de enfermedades periimplantarias. Aunque los participantes evaluaron la herramienta como buena, asignándole un valor de utilidade de 77,2 en la escala System Usability Scale (SUS) (Figura 10), se señalaron algunas sugerencias que serán analizadas para conocer la viabilidad de ser incorporadas en la propuesta de herramienta que me propongo crear en esta tesis doctoral[116].

De acuerdo con la población de estudio, clínicos dedicados al campo de la Implantología, se deben considerar cinco modificaciones adicionales:

1) considerar la relación entre el ángulo de contorno y la altura del tejido periimplantario;
2) clasificación periodontal automática en la herramienta IDRA tras completar el periodontograma en el software clínico;
3) presentación de un diagrama de flujo para ayudar a la toma de decisiones terapéuticas junto con la puntuación final definida por la herramienta IDRA;
4) integración de pruebas de precisión.

De hecho, el tema "Distancia del margen restaurador (MR) de la prótesis implanto-soportada al hueso" fue el segundo que más dudas suscitó a la hora de rellenar la herramienta. Una sugerencia fue modificar este factor por la altura del pilar protésico; sin embargo, este factor se ha ido actualizando a lo largo de los años, y el complejo supracrestal sigue teniendo una gran importancia en la predicción del riesgo periimplantario. Sin embargo, actualmente se atribuye mayor importancia al ángulo de contorno, las dimensiones de los tejidos blandos y el grosor de la mucosa han demostrado ser parámetros importantes para la salud y la estabilidad. Actualmente, la altura del pilar es una variable dependiente del ángulo del contorno [118].

Considerando una situación clínica, en el caso de una prótesis implantosoportada posterior, el complejo supracrestal del implante representa una transición de una plataforma de implante comúnmente de 4 mm de ancho a un margen cervical con una anchura aproximada de 8 mm en bucal/lingual. Si el ángulo del contorno debe ser de 30°, se puede utilizar el teorema de Pitágoras y la trigonometría para calcular la altura esencial correspondiente (figura 11). La figura 11b muestra la reducción de la altura a 2 mm, con lo que el ángulo del contorno aumenta drásticamente a 45° [118].

En cuanto al segundo tema (clasificación periodontal automática en la herramienta IDRA tras completar el periodontograma en el software clínico), esta sugerencia fue mencionada por la mayoría de los participantes, ya que la nueva clasificación es más compleja y se convierte en una limitación a la hora de completar el cuestionario. Por lo tanto, sugieren integrar la herramienta con el software clínico, y al final de completar el periograma, el vector del diagrama respectivo se llenaría automáticamente.

En cuanto a la tercera sugerencia (presentación de un diagrama de flujo para ayudar a tomar decisiones terapéuticas junto con la puntuación final), algunos clínicos sugirieron que, paralelamente a la presentación de la puntuación, se mostrara un diagrama de flujo/árbol de decisión para ayudar a los clínicos a tomar decisiones. Este árbol de decisión ya ha sido creado por el Equipo Internacional de Implantología, del que formaba parte el autor de IDRA (figura 12).

Este tipo de diagramas es muy útil ya que estandariza los protocolos clínicos y, por otro lado, también permite, de un punto de vista pedagógico, sistematizar las estrategias a adoptar en casos de enfermedad periimplantaria

En este sentido, es posible crear una herramienta de propuesta que integre los supuestos de la medicina de precisión, incorporando estrategias actualizadas para apoyar el diagnóstico y predecir el éxito del implante dental. Esta herramienta propuesta puede ser vista como una eventual actualización de IDRA, ya que fue mencionado por los autores que a medida que "factores adicionales se hagan evidentes en la literatura modificaciones del diagrama pueden ser apropiadas"[115].

La propuesta de herramienta creada se denomina Implant Failure Prediction Tool - IFPT. La IFPT aún no se ha traducido a formato digital, sólo existe como diseño conceptual. El logotipo ya fue creado por el departamento de comunicación del FMDUCP (figura 13).

Como se puede observar, seis factores son comunes al IDRA, con una aglutinación del vector "Historia de periodontitis" con el vector "Susceptibilidad a la periodontitis". Esta unión se justifica por el hecho de que queremos integrar el IFPT con un software clínico, y es interesante que toda la información capaz de clasificar periodontalmente al individuo esté reunida en el mismo vector. De los ocho factores presentados en el IFPT, seis son comunes al IDRA, que se presentan en detalle a continuación.

Partiendo de los supuestos de la medicina de precisión, ya abordados en esta tesis doctoral, es necesario comenzar a recoger datos de diferentes niveles de complejidad, desde los más superficiales, como la historia clínica, hasta los más complejos, como los datos ómicos -fenotipado profundo-. En este sentido, el IFPT se utilizará, paralelamente, de dos formas diferentes:

1) En la actualidad, ayuda en el diagnóstico precoz de enfermedades periimplantarias, concretamente mucositis y periimplantitis (figura 16), a través de los kits ImplantSafe®.
2) En un futuro próximo, funcionará como una herramienta individualizada que predecirá con exactitud el éxito del implante dental (figura 17).

Actualmente, esta herramienta reúne todas las condiciones para ser utilizada según los supuestos del tema del primer objetivo. Su cumplimentación y el cálculo del riesgo siguen la misma lógica de IDRA. Sin embargo, para mejorar la comunicación médico-paciente y facilitar al paciente la comprensión y el seguimiento de su propio caso, el resultado proporcionado por el IFPT se ofrece como señal de tráfico, además de la indicación escrita del riesgo de desarrollar una enfermedad periimplantaria. Así, desde el punto de vista del paciente, cuanto más verdoso es el diagrama, más posibilidades de éxito del implante tiene el paciente. Si aparece un vector amarillo, significa que el paciente debe modular su comportamiento para cambiarlo al nivel verde; cuanto más rojos aparezcan en el diagrama, mayor será el riesgo de desarrollar una enfermedad periimplantaria.

El cálculo del riesgo individual de desarrollar enfermedad periimplantaria se basó en la herramienta IDRA. Por consiguiente, un paciente de bajo riesgo (figura 18) tiene todos los parámetros en las categorías de bajo riesgo o, como máximo, un parámetro en cualquiera de las categorías de riesgo moderado, excepto en el vector PdC/silla. Un paciente de riesgo moderado (figura 19) tiene al menos dos parámetros en la categoría de riesgo moderado, pero como máximo un parámetro en la categoría de riesgo alto, excepto en el vector PdC/silla. Un paciente de alto riesgo (figura 20) tiene al menos dos parámetros en cualquiera de las categorías de alto riesgo.

Por otra parte, nuestro segundo objetivo con el IFPT es crear una herramienta capaz de predecir pronósticos en un futuro previsible. Actualmente, lo que está a nuestro alcance es empezar a crear un modelo de diagnóstico y pronóstico. Definir una metodología de estudio longitudinal que permita cargar en el IFPT el mayor número posible de casos clínicos ("inputs") y, a través del seguimiento de estos pacientes, identificar/diagnosticar posibles resultados clínicos de periimplantitis, mucositis o salud periimplantaria ("outcomes") a lo largo del tiempo (Figura 21). De esta forma, a medida que se procesan los datos mediante algoritmos de IA, se pueden identificar las variables/predictores con mayor significación para la determinación del fracaso del implante y, al mismo tiempo, sus respectivos pesos en el algoritmo predictivo. Esta metodología se detallará a lo largo del siguiente tema de discusión. Esta herramienta utilizará algoritmos de IA, concretamente tecnología de redes neuronales artificiales, lo que permitirá que la herramienta acumule diferentes funciones a medida que se utilice. Las redes neuronales artificiales son modelos muy flexibles y se han utilizado en medicina para explorar las relaciones entre diversas variables fisiológicas y construir modelos predictivos [154]. De este modo es posible definir un algoritmo capaz de indicar con exactitud y precisión la respuesta al tratamiento.

Para responder al punto dos y a preguntas como "¿Puedo predecir si un determinado paciente desarrollará periimplantitis?" o "¿Cómo es posible que dos pacientes con idénticas condiciones clínicas, uno presente periimplantitis y el otro no?" o como las de la figura 22 es necesario desarrollar una metodología de estudio longitudinal implicada en un largo proceso - marco de la medicina de precisión.

El concepto incorpora las siguientes ideas

1) como el proceso incluye una serie de bucles de retroalimentación (*feedback*), no existe un punto final estable de la medicina de precisión en el que, finalmente, se proporcione una atención médica precisa a los pacientes;
2) el ciclo implica que se realizan esfuerzos continuos para ser cada vez más precisos;
3) estratificaciones más finas y precisas de los pacientes pueden ser resultados provisionales del proceso global, que se recoge con el término "medicina estratificada". Un aspecto importante de este marco es, por tanto, que los datos evaluados en los pacientes se utilizan para intentar desarrollar modelos clínicamente relevantes, y que los resultados de estos análisis informan después

la evaluación posterior de los pacientes, lo que enfatiza la definición de un proceso y de la medicina de precisión como un resultado en evolución.

Como punto de partida, se recopilan datos de distintos niveles de complejidad, desde la historia clínica hasta los datos ómicos, pasando por análisis proteómicos o genómicos específicos de un fluido biológico, por ejemplo la saliva. A estas entradas de datos es necesario asociar resultados, en diferentes momentos de la evaluación, a la espera de que se produzcan los diferentes desenlaces de la enfermedad, que es la justificación de la demora en este tipo de procesos. En el caso de las enfermedades periimplantarias, habría que esperar al menos 4 años para tener un resultado de periimplantitis. Cuantos más ciclos repetidos de evaluación de pacientes, recopilación de datos, procesamiento de datos y creación de modelos arrojen grupos de pacientes, mayor resolución tendrán los modelos. En los primeros ciclos, los pacientes se clasifican en grupos de diagnóstico y/o pronóstico en función de unas pocas características evidentes (exploración física, estilo de vida, historia clínica); en ciclos posteriores se definen estratos más específicos de pacientes utilizando datos más profundos (inmunología/histología y ómica); los ciclos finales pueden llegar a centrarse en pacientes individuales con perfiles de datos específicos (figura 23).

Sobre la base de estos resultados, la metodología del estudio longitudinal en curso en la FMDUCP descrita anteriormente (figura 21) tiene la capacidad de responder a preguntas complejas que sólo pueden desentrañarse mediante estrategias de fenotipado en profundidad.

9.2.5 Conclusiones

Esta investigación, en una primera fase, analizó cómo se aplican la inteligencia artificial y las ómicas en el campo de la implantología como herramienta de ayuda en la planificación y diagnóstico de enfermedades periimplantarias. Se concluyó que actualmente ya existen protocolos clínicos bien definidos basados en algoritmos de IA, sin embargo, no ocurre lo mismo con las ómicas. Aunque está demostrado en la literatura que la combinación de ambas estrategias en protocolos clínicos permite el abordaje de la precisión clínica, ya que reduce los errores de diagnóstico y, eventualmente, permite la predicción de posibles resultados, aún no existen protocolos en este sentido.

En este sentido, se buscaron dispositivos de diagnóstico en silla actualmente disponibles en el mercado que, durante las visitas de seguimiento en paralelo con los métodos de diagnóstico convencionales, pudieran apoyar la decisión clínica en la detección de enfermedades periimplantarias. Los kits de prueba ImplantSafe®DR (dentognostics GmbH, Jena) /ORALyzer®, ya utilizados clínicamente, podrían ser una herramienta complementaria útil para mejorar el diagnóstico y el pronóstico de las enfermedades periimplantarias.

Por lo tanto, reconociendo el potencial diagnóstico de las estrategias bioinformáticas, se hizo necesario conocer la aceptación de las herramientas de evaluación del riesgo de desarrollo de periimplantitis por parte de la comunidad de odontólogos dedicados a la implantología. Entre otras conclusiones extraídas de este estudio, se identificaron las características que debería seguir la herramienta que me propuse crear.

A partir de estas conclusiones, se creó una propuesta de herramienta de predicción del riesgo periimplantario: IFPT. Esta herramienta reúne factores ampliamente conocidos y utilizados por los clínicos durante la evaluación intraoral, así como las pruebas realizadas en la consulta o el análisis proteómico a través de la recogida de saliva. Actualmente, el IFPT está incorporado en un protocolo clínico con 2 vías: 1) en la actualidad, ayuda al diagnóstico precoz de las enfermedades periimplantarias, concretamente la mucositis y la periimplantitis, a través de los kits de prueba ImplantSafe®; 2) en un futuro próximo, funcionará como una herramienta individualizada que predecirá con exactitud el éxito del implante dental.

El IFPT se está empezando a aplicarse en los protocolos clínicos utilizados en las citas de rehabilitación oral con implantes en la clínica universitaria de la FMDUCP.