Digital Immune Diagnostics for Dentistry, Implantology and Periodontology
aMMP-8 Enables the Early Detection of Active Collagen Degeneration

The ImplantSafe® DR Test System

Periodontal and peri-implant diseases usually develop gradually, and it can take decades before manifest periodontitis or peri-implantitis is diagnosed. This is because, until now, the focus has been on the extent of the degeneration (probing depth and bone loss) and not on the onset of the actual collagen breakdown process of the peri-implant tissue.

New 2018 Definition of Peri-Implantitis: What’s Healthy and What Isn’t?
The introduction of a new, global classification system for periodontitis on June 21st, 2018⁴, has brought with it a new definition for peri-implantitis.⁵,⁶ According to this definition, peri-implantitis is characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone.⁶ The onset of peri-implantitis may occur at an early stage following implant placement,⁷ and, in the absence of proper treatment, peri-implantitis progresses in a non-linear and accelerating pattern.

Quantitative Measurement of the Peri-Implant Progression Process
aMMP-8 technology with the ImplantSafe® Digital Reader system is two to three times more sensitive⁸ than the standard BOP⁷ procedure and thus offers a more reliable quantitative assessment of peri-implant “grading”, the rate of peri-implant disease progression.
Measure Active Peri-Implant Degeneration at an Early Stage

Early Detection and Progression Monitoring

ImplantSafe® DR is a tool that allows the risk of peri-implantitis and its progression to be promptly quantified.3–5 ImplantSafe® DR detects the enzyme, aMMP-8, which is classified as a biomarker for the breakdown of the collagen tissue that makes up the periodontium.3–5

aMMP-8 can be detected in peri-implant sulcus fluid (PISF), in saliva and in mouth rinse, and it can be quantified in just a few minutes with the help of the ORALyzer® digital analyzer.

This analysis allows the dynamic process of active peri-implant degeneration (APD) to be confirmed – and more importantly – allows the future risk of development and progression to be predicted.1,4–6 Since the aMMP-8 concentration decreases significantly in sulcus fluid and saliva after treatment of peri-implantitis, the aMMP-8 analysis can also be used to confirm the success of treatment.3,4

This means that you can always keep an eye on how well your treatments are working before any additional bone loss occurs.

Long-Term Success by Monitoring Collagen Degeneration

Collagen Breakdown as a Risk for Implants

Despite the high rates of short-term success, it can be assumed that with the growing number of implant placements there will also be an increase in implant losses and complications as a result of silent (subclinical) tissue degeneration.

Dental Implants: A Success Story
Dental implants are a true success story: They give your patients a new lease on (dental) life, more confidence in their appearance and a strong and secure bite. It is hardly surprising that despite costs to the patient in the range of €1,250 to €3,000 per implant, more and more patients are opting for implant-supported tooth replacement. The German Society for Implantology estimates that in Germany alone more than a million people undergo implant surgery each year.

Peri-Implantitis on the Rise
Some 87% of seniors age 64-75 say that they are satisfied or very satisfied with their prosthesis. Yet, despite impressive short-term success rates, one implant is lost every four minutes. This amounts to 140,000 cases per year, according to experts. The most common causes of implant loss are undetected inflammation and tissue degeneration processes. Peri-implant mucositis has been diagnosed in about 47% of implant patients on average, and in almost 30% of total implants, and peri-implantitis has been diagnosed in almost 20% of implant patients and in about 9% of total implants, according to a recent meta-analysis. In the end, the best protection against peri-implantitis is the early detection of the collagen breakdown processes around the implant.

Early Detection: The Best Protection
Generally speaking, the earlier the subclinical inflammation is detected, the easier it is to treat. And the sooner the implant in question or the peri-implant area receives targeted and professional treatment, the greater the chance of preventing peri-implant disease.

Pathogenesis of Periodontitis/Peri-Implantitis as a Multifactorial Disease

*Modified from Page and Kornman, 1997; Greenstein and Lamster, 2000.*

**Matrix Metalloproteinase**
- aMMP-8
  - Time: Months/Years
  - Onset of Tissue Destruction: APD (Active Periodontal/Peri-Implant Degeneration)
- Clinical Signs of the Disease, e.g. BOP, probing depth, radiograph
  - aMMP-8 can be measured with PeriSafe® PRO DRS/ImplantSafe® DRS

**Pathogens**
- Host Response, Genetic Factors
- Healthy Periodontium
- Reaction
- Collagenolysis
- Disease

**Acquired Factors**
- Local Factors
- Environmental Factors

**Healthy Periodontium**

**Other relevant terms**
- APD: Active Periodontal/Peri-Implant Degeneration
- BOP: Bleeding on Probing

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[352x814]Digital Immune Diagnostics for Dentistry, Implantology and Periodontology
By the Numbers

Early Detection of Peri-Implantitis with the aMMP-8 Test Is the Way Forward for Millions of Implant Patients

Approx. 47% of implant patients were diagnosed with peri-implant mucositis (including approximately 30% of total implants).¹

The proportion of patients with healthy, peri-implant tissues could not be determined.²

Approx. 20% of implant patients were diagnosed with peri-implantitis (including approximately 9% of total implants).³
ImplantSafe® DR Diagnostics Support the Long-Term Preservation of Implants

Sustainability of Implant Health

Patient cooperation following implant placement is a particularly important factor, especially when patients are treated with implants following periodontal tooth loss. In addition, patient recall management in the dental practice is a key factor for long-term success.

Supporting Diagnostics with the aMMP-8 Test

Early diagnosis of the onset of the collagen breakdown process, which may not be visible, is essential for the long-term preservation of the implant. If acute inflammatory processes are detected at an early stage, early preventive measures can be taken that help to avert advancing peri-implant tissue degeneration. Bleeding on Probing (BOP), probing depth measurement, and radiographs may all come too late. These measures only serve to confirm existing, in some cases irreversible, damage to the peri-implant tissue.

The aMMP-8 test complements the diagnosis from the start of the tissue breakdown process up to the point of measurable tissue or bone loss, and thus allows any necessary therapeutic measures to be taken at an early stage if the test result is positive.

Making Oral Collagen Breakdown Measurable with ImplantSafe® DR

Act – Before Complications Arise

Counteract advancing tissue degeneration with prophylactic treatment and therapeutic secondary prevention to protect your patient’s health. Secondary prevention is the treatment of a subclinical disease that has been identified to already be in progression.

Daily interdental care at home is especially important to keep teeth and gums healthy. In addition, individualized hygiene recommendations based on aMMP-8 values are an integral part of creating a personalized prevention plan for each implant patient.
ImplantSafe® DR offers an additional diagnostic option to identify patients requiring more intensive prevention measures. The aMMP-8 test for the diagnosis of active collagen breakdown is easy and only takes a few minutes.

An Important Tool for Long-Lived Dental Implants
ImplantSafe® DR measures active collagen degeneration processes by determining aMMP-8, an endogenous collagenase in the peri-implant sulcus fluid (PISF). This active form of matrix metalloproteinase-8 breaks down the tissue-supporting collagen fibers to pave the way for the upregulated migration of inflammatory cells, leading to the destruction of tissue structures. aMMP-8 is thus a biomarker for the breakdown of gingival, periodontal and peri-implant tissue.

Warning Signs of Tissue Loss
Even before changes are evident in the peri-implant tissue - usually at a reversible stage - increased aMMP-8 levels can already be detected. If aMMP-8 is permanently elevated in the PISF, progressive collagen degeneration can eventually lead to soft tissue and bone loss. In peri-implantitis, aMMP-8 levels up to 1,000 times higher than those of healthy teeth have been detected.

Regular Checkups
With ImplantSafe® DR individual implants that have an elevated aMMP-8 level can be pinpointed during regular annual checkups (e.g. 1-2x per year). A preventive treatment concept is promising at this early stage of collagen breakdown before there are even visible, clinical findings. A high level of aMMP-8, illustrated on the patient’s analysis form, can help patients grasp the importance of dental hygiene and proper dental care at home.
ImplantSafe® DR & ORALyzer®

The Digital, Quantitative aMMP-8 Chairside Test for Recall & Monitoring

ImplantSafe® DR is a digital, quantitative aMMP-8 test for the early detection of active peri-implant degeneration. Risk factors that can stimulate tissue breakdown around the implant, inflammation and thus peri-implantitis include:

- A history of periodontitis or an existing presence of acute periodontitis,
- Poor oral hygiene,
- Bacterial contamination,
- Development of oral biofilm,
- Smoking,
- Chronic diseases such as diabetes or osteoporosis,
- Various medications such as immunosuppressants and bisphosphonates,
- Bruxism,
- Alcohol or drug abuse, and
- Genetic predisposition.

As a "chairside" test ImplantSafe® DR can be performed by dental staff within only a few minutes at every recall appointment.

Selective Checkups per Implant

This biomarker technology allows you to check every single implant individually as well as differentiate between implants with limited to no collagen degeneration and those with high aMMP-8 values – and thus an elevated rate of tissue breakdown. This eliminates waiting times for laboratory test results and enables you to immediately inform the patient of the result and discuss and plan the further course of action. This immediate digital analysis allows patients to promptly visualize a numerical value assigned to their implant health, making it a perfect support feature for prevention, and for educating and motivating patients with dental implants.

Decontamination & Secondary Prevention of Peri-Implantitis

Based on the clinical picture, improved hygiene and professional anti-inflammatory treatment may be indicated, as well as more frequent recall.
Measure what can be measured, and make measurable what is not so.

Galileo Galilei, universal scholar, 1564-1641
“aMMP-8 opens the door to personalized medicine for dentistry.”

— Prof. Dr. A.–J. van Winkelhoff, Amsterdam 2018
Protecting Dental Implants and Monitoring Periodontitis Patients

Individual Implant or Tooth Measurements with ImplantSafe® DR

Screening and Monitoring of Implant Patients
Analysis of the aMMP-8 value on a dental implant in ng/ml (with ImplantSafe® DR and the ORALyzer®) indicates if the patient has an active collagen degeneration process occurring so that you can recommend the suitable measures to be taken. This allows clinically “healthy” implants at risk of peri-implant collagen breakdown to be differentiated from truly healthy implants.

Screening and Monitoring of Periodontitis Patients
The ImplantSafe® DR test can be used for individual implants as well as on individual teeth to estimate collagenolytic activity - this essentially results in two therapeutic indications. First, individual tooth testing is generally performed on teeth affected by periodontal disease with deep pockets so as to be able to assess the progression of the disease in that particular pocket. Second, the test helps differentiate therapy responders and non-responders and can identify cases where further treatment is required.

Advice for Implant Patients
Often, one individual implant is affected, while other implants are ok. In these cases, it is advisable that the component parts of the implant are immediately disassembled and decontaminated.
ImplantSafe®

The Prevention Plan for Implant Protection

As peri-implant inflammation and breakdown processes tend to be painless, the patient often underestimates the potential health risk. This means that the patient is unaware of the problem, and often the inflammatory process progresses for years. The personalized prevention plan supports patient education, saves staff communication time and improves adherence to recommended treatments.

Informing the Patient
The patient’s aMMP-8 analysis form explains how important preventive, needs-based measures are to effectively and promptly counteract an active oral collagen breakdown process (silent inflammation) and systemic interactions.

The Personalized Prevention Plan
After the analysis, you can print the result and directly transfer this to the personalized prevention plan as a sticker, and you can mark the risk category of the patient using the informative traffic light diagram. A personalized, needs-based dental hygiene prevention plan is then explained to the patient with the goal of reducing the risk of oral tissue loss around the implant as much as possible. Your professional recommendations for prevention and therapeutic measures and the optimization of hygiene care at home may also be documented.

Declaration of Understanding
By signing a consent form the patient agrees to any necessary, interdisciplinary communication with the medical specialist they are currently seeing. In addition, the declaration of understanding confirms that the practice has informed the patient of their personal risk of peri-implantitis and has made a record of this disclosure.
Your Practice Upgrade for Screening and Monitoring

Selection Criteria – An Overview of the aMMP-8 Analysis Procedure

With the PerioSafe® PRO DRS & ImplantSafe® DR product technology, dentists and physicians have the ability to measure the subclinical collagen breakdown of the periodontal or peri-implant attachment in “real time”*, allowing them to detect active periodontal/peri-implant degeneration (APD) at an early stage.

Procedure
PerioSafe® PRO DRS and ImplantSafe® DR can be analyzed by both visually confirmed qualitative analysis (elevated aMMP-8 detection: yes/no) and by quantitative analysis with an analytic report from the ORALyzer® (aMMP-8 concentration in ng/ml). Measurements can be periodically performed to show progression tendencies.

Aim
To improve the early detection of periodontal/peri-implant degeneration processes so as to counteract their progression with early, needs-based interventions, and ideally, to stop the progression altogether.

Product Range & Test Selection
To make the most of aMMP-8 prevention diagnostics, the manufacturer (dentognostics GmbH, Jena) recommends that users make an “indication-specific” differentiation between the different types of tests and sample collection variants to achieve optimum measuring accuracy when testing different types of patients.

Screening
It is recommended that patients from the age of 25 years and above have an aMMP-8 test once a year. In addition, it is advised that the test is performed at shorter intervals for patients with medical risk factors (e.g. patients with diabetes, smokers, individuals with limited mobility, etc.).

Monitoring
To reliably detect progressive collagen tissue breakdown activity at an early stage, it may be helpful to integrate an aMMP-8 analysis as a routine check at least once a year before the regular prophylaxis appointments and at each recall appointments for patients who have received supportive periodontal/peri-implant therapy. This can be very easily performed by the dental assistant or hygienist before every professional teeth cleaning with the PerioSafe® and ImplantSafe® family of products.

Evidence-Based: The Science
Compared to diagnosis via bleeding on probing (BOP), with a specificity of approximately 88% and a sensitivity of only about 29%, the aMMP-8 test is much more reliable at detecting collagenolytic enzyme activity, with a specificity of 96% and a sensitivity of up to 83%.

Note
The aMMP-8 test is not a test to confirm a diagnosis of periodontitis/peri-implantitis, but an immune analysis method to determine the level of subclinical collagen breakdown activity. This analysis should be performed periodically and is an important complementary measurement alongside pocket depth measurement.

Tip
PerioSafe® PRO DRS is recommended for use in GP practices to evaluate the risk of periodontal disease in patients with diabetes, rheumatism and cardiovascular disease.

* Results available in approximately 5-8 min after sample collection
**MRT DRS: High-Sensitivity Mouth Rinse Test**

**PerioSafe® PRO DRS**

<table>
<thead>
<tr>
<th>Type</th>
<th>Qualitative/quantitative* aMMP-8 immunoassay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Lateral flow test</td>
</tr>
<tr>
<td>Patient Selection</td>
<td>The MRT test is used for screening all seemingly healthy patients.</td>
</tr>
<tr>
<td>Application</td>
<td>Initial early detection diagnostics</td>
</tr>
<tr>
<td>Aim</td>
<td>Identification of patients with silent oral inflammation or subclinical collagen breakdown activity</td>
</tr>
<tr>
<td>What Is Measured?</td>
<td>aMMP-8 concentration in GCF from the entire mouth</td>
</tr>
<tr>
<td>Sample Medium</td>
<td>Saliva sample (mouth rinse)</td>
</tr>
<tr>
<td>Sample Collection Time in the Practice (hands-on phase)</td>
<td>Approximately 2-3 min.</td>
</tr>
<tr>
<td>Duration of Automated Analysis</td>
<td>5 min.</td>
</tr>
<tr>
<td>Result</td>
<td>Concentration of aMMP-8 level in the entire mouth (average from 28 teeth) starting at 10 ng/ml</td>
</tr>
<tr>
<td>User Group</td>
<td>Any medical &amp; dental professionals (hygienists, nurses, dental assistants, etc.)</td>
</tr>
<tr>
<td>PSI Category</td>
<td>0–1</td>
</tr>
<tr>
<td>Analysis Type</td>
<td>Screening</td>
</tr>
<tr>
<td>Advantages</td>
<td>Can complement any dental checkup or teeth cleaning and is especially suitable for diagnostics in medicine</td>
</tr>
<tr>
<td></td>
<td><strong>Implantology</strong></td>
</tr>
<tr>
<td></td>
<td>The MRT is not suitable for implant diagnostics. However, it can be used before implant placement to ensure the stability of the patient’s periodontal tissue.</td>
</tr>
<tr>
<td></td>
<td><strong>Periodontology</strong></td>
</tr>
<tr>
<td></td>
<td>In patients with obvious periodontitis it is recommended that samples are collected from the pockets directly from the area that is inflamed ( sulcus) using the PST or SST test because this offers more precise sample collection.</td>
</tr>
</tbody>
</table>

*The test is only quantitative when used for analysis with the ORALyzer®; otherwise, it is qualitative.*
### SST DR: Site-Specific Test

**ImplantSafe® DR**

<table>
<thead>
<tr>
<th>Type</th>
<th>Qualitative/quantitative* aMMP-8 immunoassay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Lateral flow dipstick</td>
</tr>
<tr>
<td>Patient Selection</td>
<td>The SST test is used for screening all patients with seemingly healthy implants &amp; for monitoring patients after periodontal/peri-implant therapy.</td>
</tr>
<tr>
<td>Application</td>
<td>Initial early detection diagnostics on implants and monitoring after treatment</td>
</tr>
<tr>
<td>Aim</td>
<td>Identification of implants or teeth with silent oral inflammation or subclinical collagen breakdown activity</td>
</tr>
<tr>
<td>What Is Measured?</td>
<td>aMMP-8 concentration in the PISF or GCF of a single implant or tooth</td>
</tr>
<tr>
<td>Sample Medium</td>
<td>Secretion from gingival pocket (sulcus fluid)</td>
</tr>
<tr>
<td>Sample Collection Time in the Practice</td>
<td>Approximately 2 min. (hands-on phase) plus a 5 min. elution (hands-off phase)</td>
</tr>
<tr>
<td>Duration of Automated Analysis</td>
<td>5 min.</td>
</tr>
<tr>
<td>Result</td>
<td>Concentration of aMMP-8 level around an individual implant or tooth starting at 20 ng/ml</td>
</tr>
<tr>
<td>User Group</td>
<td>Dentists &amp; dental hygienists</td>
</tr>
<tr>
<td>PSI Category</td>
<td>0-4</td>
</tr>
<tr>
<td>Analysis Type</td>
<td>Screening &amp; monitoring</td>
</tr>
</tbody>
</table>
| Advantages            | - Particularly suitable for dental diagnostics and can support every checkup or teeth cleaning as an immunologic prevention diagnostic for implants  
- Suitable for detecting the onset of degeneration processes around implants  
- Ideal monitoring method for identifying responders and non-responders after therapy  
- Useful complementary tool to document treatment progress |
| Considerations and Limitations |  
Implantology  
No comments  
Periodontology  
No comments |

*The test is only quantitative when used for analysis with the ORALyzer®; otherwise, it is qualitative.
Bibliography

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2. BZAK/KZBV (publisher) Fifth German oral health study (DMS V), 2016.
3. Presentation Prof. Dr. Dr. Wilfried Wagner, Mainz, 24th Congress for the German Society for Implantology in Hamburg, 25-27 November 2010.
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Overview of supplementary aMMP-8 studies


Note
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Original products to determine aMMP-8 are available from dentognostics GmbH (manufacturer) and Institut Straumann AG.