

Salivary Testing for Periodontal Disease Diagnosis and Treatment

LEARNING OBJECTIVES

After reading this article, the individual will learn:

- An effective method for dentists and dental hygienists to communicate to patients that oral health is an essential component of general health.
- How saliva and advanced DNA-polymerase chain reaction (PCR) technology can provide biological information that helps to determine periodontal disease causation and risk for future disease progression, and how to personalize therapy for each patient based on his/her specific infection.

ABOUT THE AUTHORS



Dr. Nabors was a practicing dentist for more than 38 years, during which time he developed a national reputation in the area of periodontal disease testing and treatment. Dr. Nabors treated periodontal patients using a variety of treatment philosophies: nonsurgical, surgical, laser therapy, as well as antimicrobial models. He is a distinguished lecturer at the national and state levels on personalized periodontal disease treatment and the application of molecular testing methodologies within oral medicine, and he has authored numerous articles on the subject. He can be reached at drtomnabors@oraldna.com.

Disclosure: Dr. Nabors co-founded OralDNA Labs in 2008 and serves as the company's Chief Dental Officer.



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INTRODUCTION

According to the ADA, approximately 75% of adults in the United States are affected by some form of periodontal disease, including gingivitis.¹ Periodontitis, the most advanced form of the disease in which there is active destruction of the periodontal supporting tissues, affects at least 23% of women aged 30 to 54 years.² Additionally, 44% of women aged 55 to 90 years who still have their teeth have periodontitis.² Of the US male population aged 45 to 64 years, 43% have severe periodontal disease.² That number rises to 65% in men aged 65 years and older.² In fact, in the United States alone, dental infections rank third in medical costs, behind heart disease and cancer.³

According to research presented at the 85th annual scientific meeting of the International Association for Dental Research, ethnicity and socioeconomic status can also be influencing factors for periodontal disease.⁴ The study linked periodontal disease to ethnicity and country of origin, even among immigrants who have lived for many years in the United States and have increased income and education levels. Significant differences were found among the ethnic groups, and were found to be deeply rooted in an immigrant's country of origin, where early cultural influences, such as diet, oral health practices, and environmental influences can set the stage for oral health problems later in life.

Other periodontal disease risk factors include smoking, malocclusion, diabetes, cardiovascular disease, and other systemic diseases.⁵ Clearly, periodontal disease, in all of its stages, is a microbial challenge so great that dental infections rank as the most universal affliction of humankind.

This article discusses how saliva and advanced DNA-polymerase chain reaction (PCR) technology can provide biological information that helps to determine periodontal disease causation and risk for future disease progression, and can serve as an effective method for dentists and dental hygienists to communicate to patients that oral health is an essential component of general health. Further, using this technology to personalize therapy for each patient based on his/her specific infection is discussed.

THE PERIO-SYSTEMIC LINK

Clinical research establishes that periodontal disease is an

infection of bacterial origin.⁶ The body's immune system responds to the bacteria, their endotoxins, and their antigens, thereby stimulating an inflammatory response that leads to the destruction of hard and soft tissue in the mouth.

Medical and dental research reveal that the resultant inflammatory mediators increase the risk for a variety of diseases and conditions, including heart attack, stroke, diabetic complications, and adverse pregnancy events, among others.⁷⁻⁹ The inflammatory mediators are transported to the liver, which is stimulated to produce C-reactive protein (CRP).¹⁰ CRP is produced by the body in response to injury, infection, or inflammation. Patients with periodontal disease have significantly elevated levels of CRP compared to healthy patients.^{11,12} Recent studies indicate that CRP promotes platelet adhesion to endothelial cells, a potential mechanism for the high incidence of cardiovascular events associated with high CRP levels.¹³

Several species of periodontal bacteria have been positively identified in the perio/systemic disease connection, with emerging research continuing to implicate additional species and their harmful effects on the body. For example, certain studies show that *Porphyromonas gingivalis* can adhere to, invade, and replicate within gingival epithelial cells, and induce apoptosis (cell death) of host cells, which results in the destruction of periodontal tissue.^{14,15} Other studies demonstrate that periodontal pathogens, specifically *Treponema denticola*, *Actinobacillus actinomycetemcomitans*, and *P. gingivalis*, are present in atherosclerotic plaques in coronary blood vessels.^{16,17}

HISTORY OF METHODS FOR DIAGNOSING PERIODONTAL DISEASE

Efforts toward improving the understanding of the epidemiology and prevalence of periodontal disease began in the mid 1950s, following the development of Russell's Periodontal Index (PI).¹⁸ The PI was a method for dental professionals to score, or grade, a person's periodontal condition based on a mostly visual assessment of the mouth. The criteria were based on the outward signs of periodontitis and the sequence in which they usually appear: inflammation, pocket formation, and loss of function. The major disadvantage of the PI is its reliance on subjective rather than objective

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measurement of the clinical presentation of disease. The PI scores all periodontal pockets the same, and inflammation is graded subjectively, with no apparent differentiation between gingivitis and periodontitis.

In 1959, Sigurd P. Ramfjord¹⁹ introduced the periodontal disease index (PDI). The PDI was similar to the PI, except that it added a new tool called a periodontal probe, which measured gingival pocket depths. Today, dental professionals continue to rely on a visual assessment of the patient's overall oral condition, in addition to charting pocket depths with a periodontal probe. While clinical signs and symptoms are important, they alone cannot determine causation and genetic susceptibility. They do not indicate what pathogens are present and responsible for the disease, and they do not provide insight into the patient's genetic propensity to periodontal disease. Without this important information, it can be difficult to determine the best course of treatment; whether or not antibiotics should be prescribed and, if so, the kinds of antibiotics that offer the best results in fighting the specific pathogens. This is why, in addition to probing and charting, microbial testing (bacterial inflammatory burden) and genetic testing (genetic susceptibility) should be considered an integral component in the diagnosis of periodontal disease.

CLINICAL AND BIOLOGICAL PRESENTATION OF INFLAMMATION

A sequence of events, called the inflammatory cascade, occurs during an inflammatory response. This sequence can vary depending on the type or cause of injury (ie, bacteria, heat, cold, trauma, etc), the site of injury, and the state of the body. In a localized infection, the sequence is comprised of the following physiological events: entry of infectious microbes; vasodilation of the microcirculation, resulting in increased blood flow; an increase in vascular permeability to protein; filtration of fluid into the tissue which leads to swelling; release of neutrophils (a type of white blood cell), and later monocytes (another type of white blood cell), from the blood vessels into the tissues; phagocytosis and destruction of the microbes; and, finally, tissue repair.

However, when the microbial burden becomes greater than the body's own ability to successfully fight and eliminate

the infection, such as in the case of chronic and aggressive periodontitis, adjunctive therapies such as systemic or locally applied antibiotics and mechanical debridement of the infected tissues are recommended to help the body regain homeostasis in the oral cavity.

A dilemma is that clinicians often see patients with similar clinical presentations whose disease progresses very differently. One patient may experience very little tissue destruction while another may develop severe attachment loss.

THE ROLE OF THE INTERLEUKIN-1 PERIODONTAL GENOTYPE

During the past 10 years, many studies have been published demonstrating that the severity of periodontitis in adults is closely linked with increases in local inflammatory mediators. The results of these studies have shown that most of these local inflammatory factors are controlled by the interleukin-1 (IL-1) gene, making it a key regulator in the inflammatory process and a prime candidate for a genetic association with periodontal disease.²⁰⁻²⁴ IL-1 polymorphisms are found in approximately 30% of the total population.²⁴⁻²⁶ The mere presence of the IL-1 genotype does not confer an expected periodontal disease diagnosis by itself; however, the gene has been implicated as a contributory factor in determining the severity of adult periodontitis.²⁷ Studies have shown that the presence of the IL-1 genotype is not equally distributed among all racial-cultural groups. For example, research reveals that there is a low prevalence of the periodontitis-associated IL-1 composite genotype in individuals of Chinese heritage.²⁸ At less than 3% prevalence, too few persons of Chinese heritage are positive for the IL-1 polymorphism to establish any relationship with the susceptibility to periodontitis. This low prevalence holds true for most Asian populations, whereas ethnic populations descended from northern, central, and southern Europe reveal a genotype-positive prevalence of approximately 30%.²⁶

For the first time, 2 unique salivary DNA tests are available to all dental practitioners. The MyPerioPath test is used to determine both the quality (type) and quantity (bacterial inflammatory burden) of specific pathogenic

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microorganisms associated with periodontal infections, while the MyPerioID PST test is used to identify a genetic polymorphism that affects the body's immune response. This genetic variation, which affects the production of IL-1, is associated with an increased risk for more severe periodontal infections, as well as increased risk for peri-implantitis. Both tests are intended as supportive adjuncts to conventional diagnostic methods, such as recording probing depths and the visual assessment (clinical presentation) of periodontal tissues based on swelling, redness, bleeding, and halitosis, as well as radiographic examination and a personal and family history of periodontal disease.

FUNDAMENTALS OF SALIVARY DNA TESTING

DNA testing is a relatively new science that began in 1984 when Alec Jeffreys, a genetics professor at Leicester University in England, developed what is now known as DNA fingerprinting or DNA profiling. The process was first used in forensic science to assist police detective work by positively identifying criminals by matching DNA evidence found at a crime scene to the DNA of the suspect(s). Since then, DNA tests have been developed for hundreds of applications.

Genetic tests can be broken into 5 categories: diagnostic testing, predictive testing, presymptomatic testing, carrier testing, and prenatal testing:

- Diagnostic DNA tests are used to confirm a diagnosis when a person has signs or symptoms of a genetic disease.
- Predictive tests can show which individuals have a higher chance of getting a disease before symptoms appear.
- Presymptomatic testing shows which family members are at risk for a certain hereditary condition.
- Carrier testing can indicate if an individual is a carrier of a gene alteration for a type of inherited disorder called an autosomal recessive disorder that could be passed on to one's children.
- Prenatal testing is used to screen for common genetic disorders such as spina bifida and Down syndrome. Prenatal testing is typically performed on pregnant women who are age 35 years or older, because they are at higher risk for having a child with a chromosomal abnormality.

Virtually any DNA test that uses blood can also be performed using saliva as the DNA source. Salivary DNA testing has advantages and benefits to both the healthcare practitioner who administers the test and the patient receiving the test. Saliva is easy to obtain, and it is a noninvasive procedure.

TYPES OF DNA FOUND IN SALIVA

Saliva is also known as "oral fluid" or "total" saliva because it consists of the fluid excreted from the major and minor salivary glands. Salivary fluid itself contains proteins, enzymes, and buffers that are designed to have a number of functions, including protection, buffering, digestion, and aid in swallowing.

Saliva also contains gingival crevicular fluid. In inflamed tissues, this serum exudate serves as a protective mechanism to cleanse the "pocket" of the bacteria and debris that reside within the sites. Gingival crevicular fluid contains bacteria, viruses, serum, white blood cells, inflammatory mediators, and matrix metalloproteinases. Thus, regardless of the pocket depth, the fluid that is secreted from the gingival crevice approximately 40 times per hour finds its way into saliva. Thus, saliva contains bacterial and human cells that are an excellent source for DNA.

HOW DNA IS IDENTIFIED IN SALIVA

As mentioned, saliva contains both human and bacterial DNA. Both kinds of DNA can be extracted and analyzed through a laboratory process called polymerase chain reaction (PCR).

In molecular biology, PCR is a technique for detection and elongation of DNA strands. In order to perform PCR, the laboratory must know at least a portion of the sequence of the DNA molecule it wishes to replicate. Developed in 1983 by Dr. Kary Banks Mullis, an American biochemist and Nobel laureate, PCR in its most modern form has become an indispensable technique for duplicating DNA so that it can be analyzed for the identification of hereditary diseases, as well as the detection and diagnosis of infectious disease.

In simple form, the PCR process is as follows: Once the saliva samples are received at the laboratory, a portion of the sample is syringed into separate reaction tubes and placed into a testing block. Specific polymerase enzymes and other

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components are added to each sample, which are necessary for DNA synthesis in the laboratory.

The sample-containing tubes are then placed into a thermocycler device. PCR usually consists of a series of up to 40 repeated temperature changes called thermal cycles. The thermocycler heats and cools the reaction tubes to achieve the temperatures required at each step of the reaction process. When the DNA sample is heated to 90° F, its strands separate and mix with the added components. When the components find their complementary sequences in the DNA, they bind to them; this effectively creates a duplicate of that DNA strand. The process is repeated, and those 2 DNA strands are separated and once again duplicated, resulting in 4 strands. The process is exponential—those 4 strands become 16, those 16 become 256, and so on. After approximately 30 complete thermocycles (requiring approximately 90 minutes in total), over 1 billion DNA strands are produced from the original single strand.

DNA-PCR plays an integral part in the early diagnosis of diseases and also in confirming the presence of a genetic polymorphism, or variant, which can reveal whether a person has a predisposition or increased susceptibility to a specific disease or condition. DNA-PCR also permits identification of mycobacteria, anaerobic bacteria, or viruses from several sample sources, including saliva. The basis for PCR diagnostic applications in microbiology is the detection of infectious agents and the discrimination of nonpathogenic from pathogenic strains by virtue of specific genes.

CLINICAL LAB OUTSOURCING—PROVEN IN MEDICINE, READY FOR DENTISTRY

Clinical laboratory medicine and the clinical laboratory report have become an essential component in medicine for a variety of reasons. The most compelling reason is that a physical examination that looks only at the clinical signs and symptoms of disease is not sufficient for a complete risk assessment. Many biological factors that help to determine risk can be assessed by a wide range of laboratory tests using a wide variety of body fluids. Saliva, as with blood, can now provide a variety of potential analytes that, as adjuncts to clinical signs, provide a more comprehensive risk assessment.

The primary components of a salivary DNA diagnostic test include a collection tube with a detachable funnel, a cap to seal the tube after sample collection, and a 3-mL ampule of sterile saline solution. The salivary collection process is completed in about one minute, is easy and comfortable for the patient and clinician, and is entirely noninvasive. After labeling the sample, the patient simply swishes the saline solution around in the mouth for 30 seconds and then expectorates into the funnel/collection tube. The funnel is removed; the cap is secured to the top of the collection tube. This concludes the in-office part of the test. The sample is then placed in the provided shipping box, sealed, and is now ready to be shipped to the laboratory.

All of the DNA-PCR procedures are done by OralDNA Labs, and a result report is sent to the clinician via a Health Insurance Portability and Accountability Act secure portal within 4 to 5 days. This pathogen result report contains a comprehensive interpretation of the periodontal pathogens that are detected and the quantity of detection. The genetic test report reveals comprehensive information that pertains to the (IL-1 A and β) inflammatory cytokine. OralDNA Labs is a state-of-the art accredited clinical laboratory and follows all the guidelines for accreditation that all medical laboratories are required to follow in the United States.

The clinical laboratory report (test result) should be read, shown to, and discussed with patients, as they serve to help define the diagnosis and make the condition “real” (ie, “seeing is believing”). These clinical lab reports, as in medicine, serve to help further define risk for disease and/or disease progression. It also helps patients make decisions based on biological information that confirms more specifically the disease itself and the risk associated with their specific infection. It thus serves as a persuasive means to instill the need for periodontal therapy and patient compliance in order to achieve the best possible treatment outcome. Furthermore, a “control analysis” post therapy using the MyPerioPath test also serves to confirm the efficacy of the treatment. Depending on the severity of the periodontal disease, a patient can be retested as often as deemed necessary by the practitioner; test results can be compared and monitored over time, and treatment parameters can be maintained or adjusted as necessary

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before further attachment loss has occurred.

Clinical laboratory reports have been used in medicine for decades for a variety of reasons: diagnosis, prognosis, monitoring of therapy, and treatment decision making, to name a few. The data presented in the clinical lab reports for oral diseases such as periodontal disease and eventually other disease states, helps to provide a more definitive diagnosis. Clinical signs, while still important as a means of determining the damage that has been done by the infection, do not tell what the “damaging” or causative agents actually are. While inflammation is known to cause most of the damage, the initiation of the host response and the progression of this response are known to be caused by a variety of specific microorganisms. Further, even early forms of infections can have potentially very virulent pathogens that will not be detected by clinical signs alone. Thus, a diagnosis that is based on actual causative agents in conjunction with clinical presentation provides a more definitive diagnosis and risk assessment.

This modern movement toward a biological diagnosis that includes biological risks, medical history, along with clinical history, is becoming a major theme in periodontics. Since periodontal diseases are polymicrobial biofilm infections, it is important to know which specific bacteria or combinations of bacteria are responsible for the inflammatory response in each patient. These biofilm communities are not all the same and do not create the same risk. Based on the actual species that are causative agents for these inflammatory diseases, some are high risk for attachment loss, some are considered to be associated with refractory and chronic infections, others are at lower risk, and some are more often implicated in systemic infections. This information is important to know at the earliest possible time in order to treat the actual causative agents of the inflammatory response.

The pathogens identified by the MyPerioPath test are classified in 2 taxa: facultative and anaerobic. This classification is important, as it helps determine if an antimicrobial strategy is important for each patient. Today, the use of antiseptics, locally applied medications, systemic antibiotics, and host modifying medications are all part of the arsenal for potential use. However, without knowing the virulence and pathogenic properties of the bacteria that are

found, there is no organized way to determine which patients are best suited for which antimicrobial or surgical therapy. The clinical laboratory report provides the information that will help the clinician make those decisions in a rational and organized manner.

The graphical portion of the report shows the types of pathogens present, the pathogen load, and the risk of each pathogen based on virulence factors. Longitudinal studies have shown the potential risk for each one. All of this information is important and clinically relevant to the existing disease itself and to disease progression. This information gives the clinician the ability to “target” pathogens with the goal of elimination or suppression of the pathogen associated with disease.

In addition to the laboratory result, the result report includes a relevant medical history of the patient that is provided by the clinician. This provides a more complete risk analysis for treatment planning. The medical history is an important component for establishing a treatment plan, to determine the most appropriate antimicrobial therapy, and to consider the importance of interdisciplinary therapy. Finally, the report also lists the patient’s clinical signs and symptoms. These patient characteristics further help refine the treatment planning for the patient. Clinical signs and symptoms provided by the clinician at the time of sample collection have a significant impact on the report. An ADA classification of 2 or greater may yield a suggestion of a specific antibiotic that is targeted to the taxa of the pathogens detected in the report. The purpose for this is to provide this information so that antibiotics are used based on the actual causative agent(s) rather than indiscriminately. Of course, the doctor will make the final decision as to treatment decisions and when antibiotics are necessary as a consideration for therapy.

CASE REPORT

Historical Data

The patient, a 52-year-old white male, had a history of regular dental care since age 4 years. Chart history showed repeated recommendations to have his wisdom teeth removed since 16 years old. Chart history also showed periodontal deterioration related to teeth Nos. 1 and 16 with 5 mm pockets and recession resulting in clinical attachment

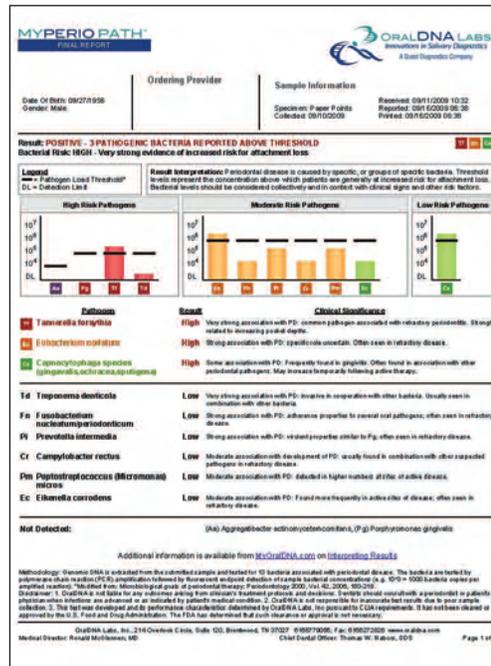
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equal-intensity contact with no interferences or inefficient use of the closing muscles upon chewing.

- Four quadrants of scaling and root planing with ultrasonic and hand instrumentation.
- Irrigation during scaling and root planing with chlorhexidine.
- Pocket disinfection with a sodium hypochlorite-based rinse disinfectant (CariFree [Oral BioTech]).
- Application of a locally applied antibiotic (Arestin [OraPharma]) in all pockets equal to or greater than 5 mm.
- Take-home oral rinse that penetrates and alters biofilm (CariFree). Chlorhexidine could be used in this situation as a home care rinse as well.
- Systemic antibiotics, Metronidazole 500 mg bid for 8 days and Amoxicillin 500 mg tid for 8 days, as an adjunct to scaling and root planing, based on the OralDNA test report.
- Physician consult to discuss the use of the antibiotic combination for this patient and his specific medical issues.
- Oral hygiene instructions with emphasis on using a power brush, dental floss, and a Waterpik (Water Pik).
- Dispensing of a high-fluoride paste to reduce risk to exposed root surfaces (Clinpro 5000 [3M ESPE]).
- Request for a 7-week reevaluation and a potential OralDNA retest based on the stability demonstrated by the periodontal charting results.

Reevaluation

The patient returned in 7 weeks to be reevaluated. He reported no complications following initial therapy, and no problems following his home care regimen or taking his prescribed antibiotics. His clinical results were excellent. He



Figures 6a and 6b. Initial MyPerioPath report results.



Figures 7 and 8. Lateral retracted views showing generalized clinical attachment loss and severe attachment loss in the posterior maxillary molar regions, and lack of visible inflammation.

had no visible inflammation and some decrease in probing depths. The 28 bleeding sites were reduced to only one. He had the greatest decrease in probing depths (3 mm) associated with the distolingual area of tooth No. 2. His post-treatment periodontal chart is shown in Figure 9.

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for geneticists as a diagnostic tool for genetic polymorphisms responsible for hereditary diseases and conditions. More recently, DNA testing has become increasingly commonplace in the medical field to assist physicians in the early “presymptom” diagnosis of patients with a family history of diseases such as those affecting the lungs and heart, degenerative disorders (such as Parkinson’s), brain diseases (such as Alzheimer’s), and certain types of cancer. Now that salivary DNA testing is available to the dental profession, it too can benefit from the clinical and hereditary insights the test results can provide.

SUMMARY

For more than 50 years, clinicians have relied primarily on the same visual and mechanical assessment methods to diagnose and classify periodontal disease. Clinical signs are simply a measurement of the past damage of a disease process. While clinical presentation and probing depths are indicators that the disease exists, these alone cannot determine the types and quantities of the responsible pathogens. Likewise, clinical signs alone cannot determine if therapy has achieved the goal of suppression of the etiological agent(s).

Genetic presymptomatic testing complements bacterial DNA testing by providing insight into the patient’s genetic predisposition to periodontal disease before symptoms appear, or when disease is already present. DNA-PCR testing of saliva can help the clinician provide an earlier and more specific diagnosis of disease based on causation. Treatment planning is also enhanced, as therapy can be appropriately modified based on both clinical and biological inflammatory factors. Finally, patient communication and case acceptance can be more readily achieved because the test reports elicit a persuasive “seeing is believing” attitude when reviewing test results with patients.

Through the use of accurate periodontal charting, medical and dental risk assessments, and other diagnostic screening tests such as OralDNA’s MyPerioPath and MyPerioID PST tests, highly personalized periodontal therapy can be developed and carried out by the general practitioner. There has never been a better time to become



Figures 11 to 13. Post-treatment photos show lack of visible inflammation and some staining from the rinse regimen.

more aware, and keep tighter control, of the periodontal status of one’s patient base. Many patients are asking dentists about the connection between periodontal health and general health. While it currently would not be appropriate to suggest a causative relationship, there is abundant ongoing research that suggests a correlative relationship between periodontal disease and other whole-body ailments.

Many patients have refused periodontal care or denied the importance of maintaining their periodontal health. The use of tools such as the OralDNA test report can assist in achieving patient acceptance of needed treatment and cooperation with the clinician to improve their periodontal health. The contents of the report and the visual presentation demonstrate that many patients have an active infection that can be stabilized if treated. Patients also provide more information about other factors that

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may contribute to their periodontal condition. Further, the OralDNA report enhances dentist-physician communication and a team approach to patient care.

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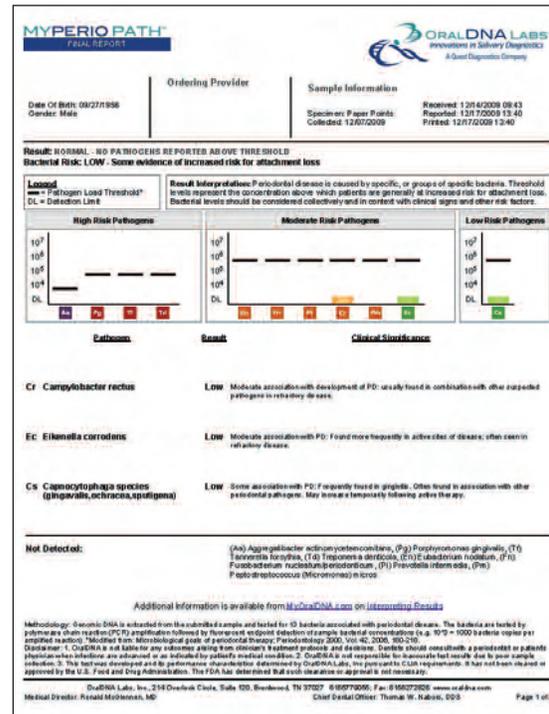


Figure 14. Page 1 of the post-treatment test report from OralDNA.

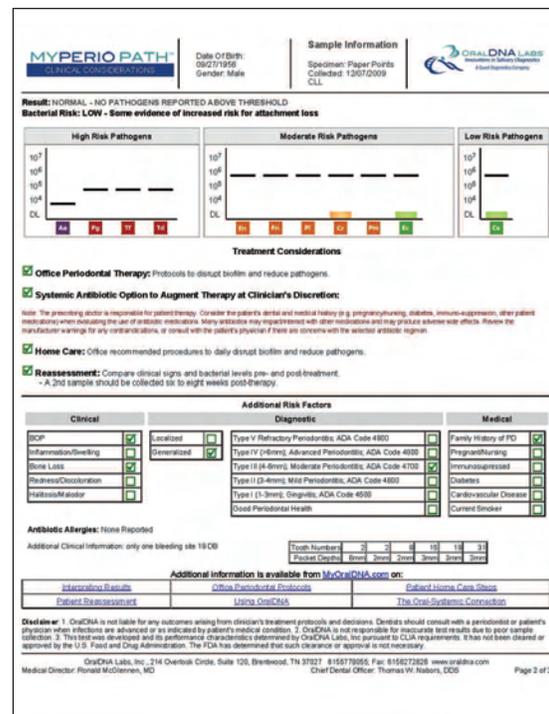


Figure 15. Page 2 of the post-treatment test report from OralDNA.

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