

PST® Genetic Susceptibility Test for Periodontal Disease
Bulletin 4

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Latest Developments

Predictive Diagnostics for the 21st Century A Discussion with Dr. Richard J. Oringer

Dr. Richard J. Oringer is an assistant professor at Stony Brook University. He is a Diplomate of the American Board of Periodontology and serves on the editorial boards for the *Journal of Periodontology* and *Journal of Evidence-based Dental Practice*. His research interests include the development of diagnostic and prognostic tests for periodontal diseases.

What are the major distinctions between “traditional” periodontal diagnostic tests and predictive tests used in risk assessment?

Our current model of periodontitis is that a microbial challenge induces a host response that can result in connective tissue and alveolar bone destruction. In addition, we realize that this disease progresses in a continuous fashion with brief periods of severe disease activity and longer periods of quiescence.

With this in mind, there is actually a big difference between traditional diagnostic tests and predictive tests used in risk assessment. Diagnostic tests are trying to identify if current disease is active in specific sites or patients. Predictive tests, on the other hand, are trying to identify people who are at risk for developing severe disease or progressing more rapidly.

Risk assessment cannot say if the person definitely will or will not develop a certain condition. This is because risk factors and risk indicators are not disease determinants, and there are no absolute “facts” about the future. Rather, risk factors are environmental, behavioral, or biological factors that have been confirmed in longitudinal studies to have a punitive impact on the disease process. The major risk factors for periodontitis, which were identified at the 1996 World Workshop, are smoking, diabetes and specific periodontal pathogens. When patients have these factors they are at increased risk for future disease progression. When these factors are removed or controlled (e.g., diabetes), the patient’s condition will improve and he/she will have a better long-term prognosis.

As we enter the new millennium we are talking less about diagnostic

tests and more about risk assessment using predictive tests. Predictive or prognostic tests help us understand if the patient is at increased risk of developing severe disease in the future. In risk assessment, the ratios we talk about are relative risk and odds ratios. These parameters are really looking at the likelihood of someone developing the condition depending if the risk factor is present or is not present. Relative risk is used in prospective or forward- looking types of trials. Odds ratios are used in retrospective trials. Both attempt to provide the likelihood or probability of disease progression given the presence of a specific risk factor.

What is the value of traditional diagnostic methods in periodontics?

Traditional periodontal diagnostic methods that include bleeding on probing (BOP), periodontal probing and radiography have been shown by Haffee and others to be poor predictors of future disease progression on an individual site basis. The most promising one is BOP as shown by Lang and co-workers. BOP is not a strong positive predictor but rather a good negative predictor of progression. In other words, the absence of BOP is a good indicator of periodontal stability as opposed to the presence of BOP predicting breakdown. Clinically this information can be of value. For example, once a patient is on maintenance, even though residual pockets remain 6mm, if no BOP is present over a number of visits, the clinician can feel more assured that the site is less likely to show advancement. Thus, this diagnostic has high negative predictive value.

On the other hand, if BOP is persistently present at a site, this is not as strong an indicator of future disease progression. In the 1996 World Workshop, a limited meta-analysis involving three studies was conducted. It was determined for a two year period during regular maintenance visits, if 63-83% of time BOP was present at the site, the patient was 2.5 times more likely to exhibit disease progression. However, common sense reinforces that the presence of BOP is not consistent with health. It is a sign of inflammation and that is some-

thing that needs to be managed in periodontal disease. Just as you would not accept chronic bleeding from your arms or legs, this should also not be accepted as “normal” in the oral cavity! In this sense, we can still use information about BOP to help us.

As for probing and radiography, their major limitation is that they are static diagnostic parameters. Therefore, the only way to identify disease progression is by performing two measurements at the same site over a specific time interval. Of course, when clinical attachment or alveolar bone loss is identified, the destruction has already occurred. This reduces the prognosis for the tooth and makes it more difficult to treat. The advent of automated periodontal probes (e.g., Florida probe) and subtraction radiography are attempts at addressing this limitation. The goal of these instruments is to detect smaller increments of change and identify disease progression earlier. Whether these refined measurement tools are superior to traditional diagnostic methods has not been definitively demonstrated at this time.

The ideal clinical tool would identify active disease in the pre-clinical phase during the biologic onset but before significant periodontal destruction has occurred. As there has been a tremendous increase in our knowledge regarding the pathogenesis of periodontal disease in the last thirty years, there have also been many attempts to develop such a tool. These attempts have fallen into three categories: microbial assessment (eg., measuring bacteria), biochemical markers (eg., measuring host response) and risk assessment (eg., genetic susceptibility). Genetics have received the strongest attention in recent years.

What is the value of microbial assessment in periodontics?

There have been three major areas of emphasis for microbial assessment. These include the “gold standard” culture methods that provide a broad bacterial spectrum and antibiotic sensitivity; DNA probes, which analyze the fragment DNA of bacterial species; and enzyme assays, that detect enzyme activity commonly associated with the microorganism. There are commercial services available for these tests worldwide but they are more limited within the USA. Microbial testing may be appropriate in:

- Patients not responding to traditional therapies
- High risk, medically compromised patients
- Aggressive periodontitis cases

The challenge for microbial assessment is identification of which specific bacteria are responsible for disease in a specific patient. In this regard, Socransky and co-workers used DNA probes to examine subgingival plaque samples and categorized forty organisms into complexes identified by a specific color, e.g. the “red” complex. In his recent article comparing healthy and diseased patients, it was shown that higher levels of the red complex organisms are associated with increased disease progression. Both subgingival and supragingival scaling and root planing reduce the levels of red complex organisms

but not the proportions. In other words, the absolute number of organisms is decreased but they are still present. What still needs to be determined is the specific microbial thresholds associated with disease initiation and progression.

The limitation of microbial assessment relates to our lack of knowledge regarding the direct causal relationship between the presence of specific pathogens and disease progression. Abundant evidence reinforces this causal relationship between bacteria and disease but not for an individual patient or site. Given the multifactorial nature of periodontitis and the multiple bacterial players this can be a formidable task. Adding to this complexity is the fact that periodontal pathogens are evident at both healthy and diseased sites. We don’t know the threshold that the individual patient can accept and there is a high likelihood this differs based on host response. In other words, the threshold is most likely patient dependent.

What is the value of biochemical markers in periodontics?

Probably the greatest advance in recent decades has been our increased understanding of the important role the host plays in periodontal disease. For many years the predominant focus was on bacteria. This is justified since the bacterial challenge is the initiating event in periodontal disease. However, it is actually the host response that, in an effort to protect us, causes the destruction. Therefore, investigators have evaluated components of the host response, found in gingival crevicular fluid (GCF), as potential diagnostic measures of active disease. To this end, a number of mediators have been examined. The mediators studied most extensively include:

- Prostaglandin E2 (PGE2), an inflammatory mediator involved in bone resorption and connective tissue breakdown
- β -Glucuronidase and elastase, enzymes released by neutrophils, the predominate cell type in the sulcus
- Aspartate aminotransferase (AST), an intracellular enzyme present in almost all cells that is released to the extracellular environment during periods of tissue injury

The major limitation of biochemical tests is that they do not reliably distinguish between gingivitis and periodontitis, because elevated levels of the mediators are associated with gingival inflammation. Recently, investigators have begun to evaluate mediators associated with bone destruction. The identification of minute bone changes via elevated GCF levels of a bone destruction marker could allow for earlier treatment interventions. C-telopeptide pyridinoline cross-links (ICTP), for example, is a breakdown product of Type 1 collagen that is specific to bone. Giannobile and co-workers are actively pursuing this research. However, at this time no GCF-based diagnostic test has been routinely utilized for the diagnosis of periodontitis.

What is the value of risk assessment in periodontics?

Risk assessment and genetics have received a lot of attention and excitement in the last few years. A clear departure from diagnostic tests, this idea focuses on increased risk or susceptibility for future progression. The genetic influence on periodontal disease has been well documented. Loe and co-workers determined in their landmark study that 11% of the Sri Lanka population didn't have disease progression and 8% had aggressive progression, even with equally high levels of plaque and calculus. In other words, the bacterial challenge did not correlate with disease progression. These findings reinforced that there are individuals who appear to be "resistant" to periodontitis, having high levels of plaque but little disease. Conversely, there are also individuals who have little plaque and calculus but advanced levels of disease. Genetics regulating the body's response is probably the reason.

The emphasis in recent years has been on evaluating gene polymorphisms in specific cytokines including interleukin-1(IL-1), tumor necrosis factor-alpha (TNF α), and interleukin-6 (IL-6) that have all been associated with periodontal destruction. Genetic polymorphisms arise when a change occurs in a single base pair of DNA that may subsequently result in a different type of host response. IL-1 is one of the cytokines that has been studied extensively and appears to be an important mediator in the pathogenesis of periodontitis. It is known that lipopolysaccharides (LPS) or gram-negative bacteria stimulate monocytes and macrophages to produce IL-1 and that IL-1 plays a central role in bone resorption and destruction of extracellular matrix via up regulation of matrix metalloproteinase (MMP) activity.

This research has resulted in the PST Genetic Susceptibility Test, which identifies a specific polymorphism located on the long arm of Chromosome 2 that regulates IL-1 production. Originally, DNA was collected via blood but it can now be collected via cheek cells. This makes the PST test much more convenient and easier to discuss with patients. The test is based on the polymerase chain reaction (PCR) technique and the results report the presence of allele "1" or "2". The allele 2 has been associated with chronic periodontitis. If there is an allele 2 in both positions on the IL-1A and IL-1B genes it is considered a homozygous genotype; if there is only one allele 2 in both positions it is considered heterozygous. Both homozygous and heterozygous combinations are considered IL-1 genotype positive.

This all started with a landmark study by Kornman and co-workers. This group reported that there was a higher percentage of IL-1 genotype positive patients in the severe periodontitis group than in the slight to moderate cohort. More importantly, in looking at it cross-sectionally at different age levels, it appeared that a higher percentage of IL-1 genotype positive individuals were exhibiting significant disease as much as twenty years earlier compared to genotype negative individuals. In addition, other early studies demonstrated that positive IL-1 genotype patients, both heterozygous and homozygous for allele 2, tended to secrete more IL-1 β from their monocytes, neutrophils, and

macrophages when stimulated with a challenge.

Over the last few years multiple studies have provided additional evidence that an association exists between these specific polymorphisms and the severity of periodontitis. However, not all studies have demonstrated a positive correlation. This is expected since different investigations may use various study designs and not adequately control for confounding factors. These are factors that may independently contribute to the progression of disease or that effect the ability of other factors to cause disease (e.g., smoking, poor oral hygiene). Initially an investigator may look at factors independently, even though multiple factors might be influencing it or interacting in some way. Statistical tests such as multivariate analysis help us better understand how these factors relate to disease and to each other. For example, McDevitt and co-workers found that age, former smoking history and a positive IL-1 genotype were all associated with an increased risk of severe periodontitis. Interestingly, in the McGuire and Nunn study, they found that risk of tooth loss could not be determined by any of the traditional clinical parameters, but only by looking at IL-1 genotype and smoking status. They also showed that there was no correlation between IL-1 genotype and the patients' self-reporting their family histories, so the PST test information is giving the clinicians something they cannot learn any other way. Furthermore, the multiplicative effect found between a positive IL-1 genotype and heavy smoking in the McGuire and Nunn study was our first glimpse that an interaction could exist between these risk factors. Again, knowing there might be a synergy between a positive IL-1 genotype and smoking provides additional valuable information you cannot get without the PST test.

What is the association between the IL-1 genotype and traditional diagnostic measures such as BOP?

Lang, Tonetti and co-workers reported a significant chance of increased BOP over the maintenance period in IL-1 genotype positive, non-smoking patients. In addition, using the latest recall visit, the IL-1 negative subjects exhibited a significantly lower percentage of BOP. We know from the World Workshop meta-analysis mentioned previously, that persistent BOP might be associated with an increased risk of disease progression. Even though it is not as accurate a predictor as the absence of BOP, the presence of BOP at regular recall visits is indicative of inflammation and not consistent with periodontal health.

Goodson and co-workers recently supported this observation in an experimental gingivitis model. Healthy individuals with no clinical signs of periodontitis stopped brushing their teeth for three weeks to allow gingival inflammation to begin. They found higher IL-1 levels in GCF in IL-1 genotype positive individuals versus the genotype negative subjects. These results suggest that IL-1 genotype positive patients may produce IL-1 more quickly than genotype negative individuals, which may lead to more inflammation. We know that certain pathogens thrive in the presence of inflammation, so in addition to accelerating tissue destruction, more IL-1 may lead to the presence of

undesirable bacteria. Further studies are needed to validate this concept. Overall, these studies suggest that the IL-1 genotype status may relate to accepted risk factors and to traditional diagnostic parameters including BOP.

What does risk assessment mean in everyday practice?

Given the evidence we have, this risk information is predominantly useful to increase compliance in our patients, especially where we are concerned about future progression or initiation of disease. For example, in patients continuing to breakdown, you may say that you already know they have disease and that they are not responding, so what is the purpose of the test? The test will provide objective information so that you can explain to your patients that this could be one reason for the progression of their disease. This dialogue reinforces to your patients that you care and are trying everything you can to understand the etiology of their conditions.

What about periodontally healthy individuals with a family history of periodontal disease? Although patients' self-reporting their family histories did not directly correlate with the genetic test results in McGuire's study, if you have patients reporting periodontitis in their families, the PST test could certainly provide objective information as to whether they may be at genetic risk for the disease, and help improve compliance. For example, in a college-age adult where compliance may be less than ideal, this test might help bring the message home that this is disease management for a lifetime. However, additional studies are needed to determine the absolute risk of disease initiation associated with a positive IL-1 genotype status in a periodontally healthy individual.

So the question is whether you go ahead with PST testing or not? Ultimately, practitioners have to use the available data to determine the usefulness of the test given the specific needs of each individual patient. New information regarding the PST test is rapidly emerging, but we still do not have all the answers. For instance, whether certain therapies are indicated based on IL-1 genotype status has not been fully demonstrated. There was a recent study by DeSanctis and co-workers on guided tissue regeneration (GTR) treatment where they found the IL-1 genotype positive patients lost more attachment over a four year follow-up period than genotype negative patients. This suggests that maintaining the GTR result will require more compliance and supportive care in high risk patients. In addition, Axelsson recently presented results for both IL-1 genotype positive and negative non-smoking patients in long-term maintenance that demonstrated, if strict compliance was observed, the positive patients did not respond any differently than the negative patients. However, IL-1 genotype positive smokers lost 3 times as many teeth compared with smokers who were genotype negative, even with strict compliance.

What do you foresee as the major challenges for these technologies?

A critical issue is the perceived need by practitioners for these tests. In this regard, the fact that these technologies do not provide the practitioner immediate results regarding patient outcomes has reduced the utilization of these tests in clinical practice. Educational programs such as these Bulletins are vital to increase the dentist's understanding of the natural history of periodontal diseases and the concept of varying degrees of susceptibility based upon genetic background. Research is also needed to confirm that utilization of these technologies improves treatment outcomes. The difficulty is that these studies are expensive to conduct since they require large groups of patients to be followed for very long periods of time. However, completion of these studies would help the acceptance of these technologies by insurance companies, patients and practitioners.

It was previously believed that one "magic bullet" might explain all risk for disease. It is now recognized that combination testing will be necessary to examine aspects of the microbial burden, host response, and genetic background of the patient. This information will then be used along with traditional clinical parameters (e.g., probing depth, attachment level, furcation involvement, and mobility patterns) to develop a patient profile. Thus, acceptance of a more probabilistic approach to disease management is needed in periodontics instead of the conventional "treat the destruction only" approach. Tonetti and Lang have reported on a risk assessment model that attempts to quantify the magnitude of risk associated with specific factors at the tooth, site and patient levels. These investigators are currently evaluating this model in longitudinal clinical trials.

Practitioners already use risk assessment in practice when they consult with their patients regarding oral hygiene, smoking cessation, and diabetic control. Along with these confirmed risk factors, the PST test provides the practitioner additional information to help characterize a patient's degree of susceptibility. However, additional information is needed to determine how these factors interact with each other and the relative magnitude that each factor contributes to disease progression.

So where are we in the new millennium? We recognize that patients present with different degrees of susceptibility. Practitioners should utilize risk assessment methods to help identify factors which can be reduced or eliminated (e.g., bacterial challenge, smoking, diabetes) or are currently beyond our ability to control (e.g., genetic predisposition). This information can then be used to direct therapy, educate patients, and improve treatment outcomes.

Thank you.

Incorporating PST Testing into Clinical Practice

A Discussion with Dr. Jacques Charon

Dr. Jacques Charon is in a private practice focused on periodontics in Lille, France. He is most interested in treating the very severe cases often referred to as “hopeless”. His training has been both as a clinician and researcher in cellular immunology at the National Institute of Dental and Craniofacial Research (NIDCR). He was the first to demonstrate IL-1 activity in the gingival fluid. Dr. Charon is committed to an evidence-based practice, trying to apply the data published in the scientific literature to private clinical practice.

What prompted you to begin using the PST test clinically?

When I first learned about the PST test it was of obvious interest scientifically. When you contemplate that there are over three billion base pairs identified within the human genome and the impact that a single base pair transition could have on the resulting host response and gene production it can be overwhelming. Even more striking is the identification of this single base pair transition. These genetic (single nucleotide) variations can be described simply as one of the following: a deletion, an insertion or a transition of the alleles within the promoter region of the gene (e.g., IL-1A and IL-1B) that can result in altered gene expression and altered proteins. The genetic science is fascinating but is of little practical use unless we understand how this information impacts the pathogenesis of disease. Then we can realistically discuss prevention.

To this end, there have been great strides in our understanding. The prevalent thinking of the 1960s advocated that everyone was equally susceptible, and without good dental hygiene, would develop gingivitis. In turn, without dental treatment, gingivitis would automatically advance to periodontitis. In the 1980s, we further refined this model by moving from the concept of “equal susceptibility” toward more “individual susceptibility” advocating that 5% of those exhibiting gingivitis would not subsequently experience attachment loss; 80% would progress moderately showing some attachment loss and moderate clinical symptoms with another 15% showing advanced clinical symptoms and severe attachment loss. This period focused on the causal role of bacteria in this trajectory and diagnostic tools to identify the periodontal pathogens. Now, the model of this century incorporates the central role of risk for future progression and how inflammation directs the disease process. The interaction of the host response with LPS activated monocytes, endothelial cells, epithelial cells and neutrophils can either diminish or accelerate the anatomical destruction.

Beyond my fascination with the genetics and the great strides in understanding the pathogenesis of periodontal disease, the scientific data validating the role that a specific IL-1 composite genotype plays

in identifying individuals at an increased risk of developing severe periodontal disease was most compelling. The odds ratios ranging from a 6- to 19-fold increased likelihood of more advanced progression are noteworthy, especially against the backdrop of other widely accepted periodontal risk factors such as smoking (5x) and diabetes (2.3x). These ratios are even more compelling when we look at other diseases such as cardiovascular disease with the cholesterol risk factor having an odds ratio of 2.4x. This data was only further reinforced when coupled with the biological explanation that individuals positive for the IL-1 genotype produce 2-4 times more IL-1 β in response to bacteria. Again, this evidence supports our most current understanding of the pathogenesis of disease. The scientific evidence is solid with over fifty new publications specific to the IL-1 genotype in the last four years. The data is mounting and is remarkably consistent that genetics and smoking behaviors account for greater than 80% of severe disease. With such strong scientific support it all makes too much sense to be ignored. Motivated by the science and its “fit” with our most current understanding, I began using the PST test. My focus has been to better understand how this new information could best be applied to my clinical decision-making and what would be necessary to make this a routine part of my practice.

How is this genetic information of added value to your clinical decision-making?

One of my first observations was that I couldn't predict who would be genetically susceptible and at increased risk. As you will see in Figure 1, the patient you would strongly suspect is genetically susceptible and at increased risk for disease progression would be the one on the left. However, this patient was IL-1 genotype negative, a non-smoker with multiple caries. Obviously, this patient needs dental treatment, but the prognostic question is what is his likelihood for future progression? Predicting the likelihood of future progression is the fundamental role of risk factors, and in this patient's case, future risk is not unusually high. On the other hand, I would have predicted that the patient on the right with no caries and a generally healthy appearance would be at low risk for future progression. However, this patient was IL-1 genotype positive. Coupled with high stress, this patient was at high risk for future progression. Without the PST test, it would have been difficult to impossible to have identified this patient as “high risk” since I can think of no objective information I have readily available that would do that for me. So clearly the test provides me additional valuable information not accessible by other means. McGuire and Nunn have shown us that traditional prognostic parameters are of limited value especially in difficult cases and diagnostic tests only tell

PST

us about disease activity or status at a specific point in time. Understanding which treatment option may be best for our patients demands that we assess the individual patient's risk and long-term prognosis.



Low Risk

- IL-1 Genotype –
- Non-Smoker
- Caries



High Risk

- IL-1 Genotype +
- Stress
- No Caries

Figure 1. Can you visually predict?

Furthermore, the strong links between periodontal inflammation and other inflammatory diseases/conditions reinforces my need to understand who among my patients has the propensity to overproduce IL-1, the core inflammatory agent. Knowing this information now influences my clinical judgment. Patients who are obvious candidates for PST testing include:

- Patients contemplating extensive prosthetic restoration
- Patients undergoing orthodontic treatment
- Biological relatives of patients with severe periodontal disease
- Biological relatives of patients who tested positive for the IL-1 genotype
- Patients at high risk for cardiovascular disease
- Pregnant or female patients planning pregnancy
- Patients with severe periodontal disease
- Patients exhibiting early signs of periodontal disease

With the emerging data supporting the synergy of a positive IL-1 genotype and smoking, I would also advise testing smoking patients who, as a result of this interaction, may be at even greater risk for more rapid progression. In Figure 2, I have attempted to illustrate the risk assessment I conduct on my patients to determine their level of risk for future progression. In my assessment model I concentrate on six measures of risk:

- Genetic predisposition via the PST test
- Smoking status
- Stress level
- Medical factors
- Extent of dental caries
- Presence of acute necrotizing ulcerative gingivitis (ANUG)

By characterizing my patients accordingly, I am able to quickly and more objectively assess their risk for future progression and adjust their treatment, maintenance and compliance activities on an individual

patient basis. We have long understood that patients are not equally susceptible but our practical application of that knowledge has not reinforced that understanding. We still treat and maintain patients as if they are all equally susceptible and rationalize it as “quality care”. We all know that targeted care is most cost-effective but we don't behave as if it is. The PST test is the only objective measure I have to identify the genetic susceptibility of an individual patient. It allows me to align my treatment plan in accordance with our most current understanding of the disease process and recommend the most cost-effective therapy. Scientific evidence has clearly differentiated disease trajectories and genetics is key to that distinction. For me, the question is really not why should I use it but rather how can I justify not using the test?

	Low	Moderate	High
IL-1 Genotype	Negative	Negative	Positive
Smoking	No or stopped for length of time	Less than 10/day	More than 10/day for length of time
Stress	No	Occasional Resolved	Acute stress plus anxiety
Medical	No	Ear, nose, throat	Virus, Diabetes, Aids, Trismomic Chemotherapy Immunosuppressive
Caries Activity	More than 15	From 5-14	Less than 5
ANUG	No	Chronic gingivitis	Yes

1 2 3 4 5
 Low ← Moderate → High

Figure 2. Risk assessment profile.

Clearly you are an advocate for the added value of PST testing, but how have you effectively incorporated this into your everyday clinical practice?

First the sample collection procedure must be simple for the staff and comfortable for the patient. There have been several iterations of the DNA collection technique from blood to saliva to cheek cell. These modifications have continuously addressed the issues and improved this procedure to increasingly meet these goals...simple, comfortable, convenient. The cheek cell technique can be completed chairside requiring little time and effort for collection. The sample is then sent to the laboratory and results mailed back to you within a few days. The laboratory report clearly identifies whether the patient is IL-1 genotype “positive” or “negative”. This information coupled with support materials provided by the laboratory (or their representatives) help

supplement our interpretation of these results and what this means to the individual patient. My understanding is that this is generally the way it works in Europe and the USA. Just spread the one-time cost of 115 Euros across the “lifetime” of the patient in your practice and it is very little to pay for the value of the information it offers both short- and long-term.

One of the easiest ways to begin is with new patients. An introductory letter is sent to patients or potential new patients to create periodontal awareness, especially given that prevention is possible. It simply defines the six risk factors and lets them know there are options for those at risk. This is a “practice builder” and an example of such a letter is presented as Figure 3.

Figure 3. Introductory letter.

Ladies and Gentlemen,

You are probably in a periodontal office because your gums have receded and your teeth appear long.

We think you would have no doubt preferred not to have this happen. We have the pleasure to inform you that there now exist means to effectively prevent receding gums/long teeth. We know that some individuals are more “at risk” than others of developing periodontitis. The consequences are that your gums continue to recede, your teeth look longer and eventually teeth are lost. These individuals have one or more of the following six characteristics:

- Family history of periodontal disease
- Acute stress and anxiety
- Excessive smoking
- Infection sensitivity or systemic disease
- Resistance to caries
- History of gingival infection or gingivitis

A simple and relatively inexpensive program helps to lower the risk of having receded gums and long teeth. Our team is especially trained to help you benefit from this preventive program. This also includes your family and friends. You can all keep your healthy, beautiful teeth for a lifetime. It is always better to keep your teeth than to lose them unnecessarily.

Do not hesitate to ask for more information about our program for periodontal prevention at your next office visit.

Very periodontally yours,

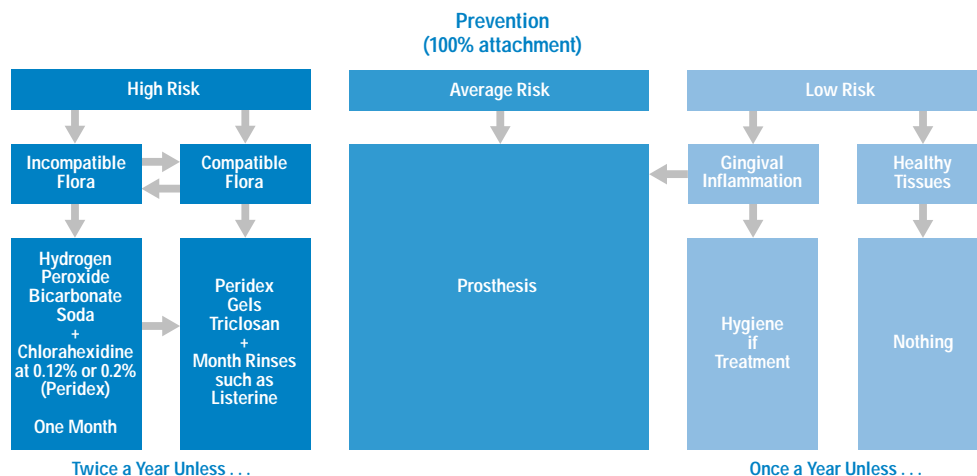


Figure 4. Treatment algorithm.

Once an office visit is set, my initial consultation is aimed at establishing a climate of confidence and competence with the patient. This is accomplished primarily by the attitude and actions of the office staff and me, including the use of risk assessment to develop the best most cost-effective treatment plan for that individual patient. With these goals in mind, we schedule the following:

- Entrance (Educational Materials)
- Clinical Examination
- Complementary Examinations
 - Radiological
 - Microbiological
 - Biological (PST Testing)
- Risk Assessment

As illustrated in Figure 4, I incorporate this information into an algorithm that helps visually depict for patients that they are on a specific course of treatment tailored to their individual patient profiles and aimed at preventing or minimizing the further anatomical destruction. This algorithm outlines the examination and risk assessment process leading to an individualized prophylaxis program.

This same basic approach can obviously be adapted to test patients already within the practice who are in maintenance programs or considering expensive implant, complex restorative or orthodontic reconstructions.

What were the biggest obstacles you encountered with the PST test?

The biggest initial obstacle was Jacques Charon. Any change requires personal commitment. Until I felt competent enough to be confident with this approach and was able to recognize the value this information provided, I had difficulty recommending the test and hav-

ing patients' accept being tested. Initially, I developed competence intellectually. As I said earlier, this all makes too much sense logically not to be able to do that! However, that intellectual competence only helped get me started. It wasn't until I gained clinical experience through using the test and discussing it directly with patients that I became confident. Knowledge and experience together translate to confidence and competence. It is surprising how reassuring it is to patients to better understand their personal risk profiles. Certainly it cannot hurt

and could potentially help patient compliance and motivation. We all know this is a big issue historically that persists today.

Other than that, there are issues regarding ease of use as we mentioned previously, office staff training, and patient concerns with privacy and all that entails. Most of these obstacles are readily workable once the doctor, as an individual, gets through his/her "learning curve".

Is there anything you would like to add to this discussion?

Most of this discussion has revolved around the treatment and likelihood of future disease progression. Now I would like to underscore the tremendous leaps of knowledge emerging regarding the relationship of periodontal disease to other medical diseases. I think we are at the forefront of a new understanding about the active role of inflammation in most chronic diseases and the role genetics plays in regulating the inflammatory response. Yes, there is most likely an "initiating event" for the onset of disease, but how the body deals with that event determines how severe the disease becomes. We can no longer isolate what happens in the oral cavity from the rest of the body. For instance, scientific data is clearly linking premature births (before 32 weeks at weights less than 2500 grams), cardiovascular disease and respiratory diseases with periodontal disease. It is most obvious to me that genetics will be the common denominator underlying these connections. Genetic information is now available that we can objectively use to help us reliably predict those who are at risk for increased inflammation because of a hyperinflammatory host response. This information is not only beneficial in managing periodontal disease but in the overall health of the patient. The question for me is not "so what?" but rather "why not?"

Thank you.

The Role of Genetic Risk Factors in Periodontitis and the Overall Health of the Patient

A Discussion with Dr. Kenneth Kornman

Dr. Kenneth Kornman is Chief Scientific Officer at Interleukin Genetics, Inc.

Why should we be interested in risk assessment?

There are, of course, no facts about the future, only probabilities. In clinical practice we make therapy decisions based on estimates about the future of each case, but most of those estimates are unconscious. Our treatment decisions for a specific individual patient are based on the answers to the following two questions:

- How severe is the past tissue destruction?
- What is the risk for future disease progression?

Risk assessment, either conscious or unconscious, is the approach we use to answer the latter question. With that in mind, let me now provide a brief historical context to put this in perspective. Our primary message over the last thirty years reinforced the role of plaque control as the only consistent determinant of periodontal disease. However, there have been several fundamental changes to our understanding of this disease that have impacted this traditional concept. These changes can be summarized as: differential susceptibilities (not everyone is equally susceptible) to the onset of disease, the prevalence of different severities of the disease and the emerging links between periodontal disease and other medical diseases or conditions. Prior to the 1980s we were taught that everyone was equally susceptible to periodontal disease and that approximately 70% of the adult population had periodontal disease. In the 1980s, it became increasingly apparent that the prevalence of periodontal disease needed re-examination. We now understand that 70% of the adult population exhibits gingivitis with approximately 30% experiencing only localized periodontitis. In fact, only 8-15% of the worldwide adult population can be characterized as having severe generalized periodontitis. Even though these percentages are lower than we originally thought, when they are applied to adult population figures, periodontitis still represents a major health issue.

With this background, why should we be interested in risk assessment? Let's start by what we know. We know that:

1. A subset of individuals is at increased risk for severe generalized periodontitis.
2. Periodontal therapy and maintenance care do not prevent tooth loss in certain individuals. As reported by Hirschfeld (1978), McFall (1982)

and McLeod (1997), 78-84% of patients will experience minimal disease progression and tooth loss (average tooth loss= 0.5-1). Conversely, this means that 16-22% of the patients experience moderate to severe disease progression losing on average 5-14 teeth.

3. Severe generalized disease is more difficult to treat and is a patient characteristic and not a tooth or site characteristic.
4. These patients can be identified by a small set of risk factors that, if present, identify individuals more likely to have severe generalized disease and less likely to respond to therapy.

With this increased knowledge, we are now in a better position than ever before to use both the traditional parameters for assessing past destruction of the disease coupled with risk information regarding future progression of the disease to improve our treatment decision-making. Furthermore, improvements in disease management may have implications not only for the oral health but the overall health of the patient, although this conclusion remains to be proven.

What do you see as the small set of risk factors that predict future disease progression?

In addition to certain bacterial patterns being associated with differing degrees of disease expression, the severity of periodontitis is the result of multiple factors that influence the inflammation. Specific bacteria activate inflammation in the periodontal tissues; however, the degree of inflammatory response is altered by the body as impacted by the presence/absence of genetic and environmental factors (e.g., smoking). These interactions contribute to the clinical disease severity expressed. The key to this new understanding of the biology and mechanisms involved in the pathogenesis of periodontal disease centers on what happens in the tissues. Specifically, this refers to the biochemical interactions that create homeostasis and the pathologic mechanisms at work in the connective tissues and in the bone along with the immuno-inflammatory processes. These interactions are initiated by the presence of specific periodontal pathogens. Periodontal therapy is designed to reduce and control the pathogens. It is important to consider, therefore, how certain characteristics of each patient influence how the bacteria interact with the biochemical processes in the tissues. The risk for future disease progression is influenced by the control of bacteria, and factors known to alter the body's response to the bacteria, e.g., genetic susceptibility, smoking, and systemic diseases such as diabetes.

With this model in mind, let's further examine how individual genetic variations impact periodontal disease. Specific bacteria are essential for the onset of periodontal disease. Many studies throughout the world have substantiated that three chemicals in the tissues are consistently associated with more disease severity or actively progressing disease. These are IL-1, PGE2, and MMPs. Concentrating on IL-1, recent studies comparing bone loss to IL-1 level in the GCF reported a direct relationship. The higher the IL-1 level the greater the bone loss. Lorenzo and co-workers have examined the critical role of IL-1 in a mouse model looking at its role in bone loss during estrogen depletion (e.g., menopause). The mice with intact IL-1 systems were ovariectomized to simulate estrogen depletion and the animals lost substantial bone density. However, mice with blockage in their IL-1 systems exhibited no bone loss following estrogen depletion. This suggests the essential role of IL-1 in bone loss following an initiating event such as estrogen depletion. Increased IL-1 activity has also been associated with the development of spontaneous arthritis as reported by Horai and co-workers. Using specially developed IL-1 receptor-antagonist knock out mice, the IL-1 activity was increased many-fold. With this heightened IL-1 activity, greater than 80% of the mice developed arthritis in less than eight weeks. Bresnihan and co-workers have reported that clinically treating arthritis patients with IL-1 blocking drugs has significantly reduced the bone erosion.

Similarly, Assuma and co-workers reported the essential role of IL-1 in a monkey periodontitis model. The test group was treated with specific chemicals that block IL-1 and another chemical to block TNF α . In spite of the heavy bacterial challenge, the group with blocked IL-1 and TNF α exhibited a 67% reduction in osteoclasts and a 60% reduction in bone loss.

From twin studies we know there is a strong genetic component to the disease where 30-60% of the clinical severity of disease could be explained by genetics. It is now known that there are specific variations in the IL-1 genes that cause excessive production of IL-1 in response to a bacterial challenge and furthermore, these variations run in families. Periodontal studies have documented that individuals with these IL-1 gene variations have increased IL-1 levels produced by their white blood cells and present in GCF, as well as BOP.

With literally thousands of chemicals involved in the metabolism of periodontal tissues why is IL-1 being singled out? The reason may be that IL-1 sits at a "pivotal" position of multiple biochemical cascades and therefore has greater potential to amplify tissue responses. Our research suggests that it is unusual in that IL-1 has great leverage power in certain diseases. IL-1 is a critical part of the destruction of bone and connective tissues and therefore, is an important risk factor for periodontal disease. IL-1 gene variations:

- Increase IL-1 levels in gingival tissues
- Alter the progression of periodontitis
- Alter the response to therapy

Specifically, how do these IL-1 gene variations increase the risk for progression of periodontal disease?

I would identify at least three ways in which IL-1 gene variations influence the risk for future disease progression. Variations in the IL-1 genes amplify the body's response to an initiating event such as bacteria; influence disease trajectory; and alter response to therapy.

We have already discussed that IL-1 is a critical part of the destruction of connective tissue and bone. Figure 5 summarizes this biochemical cascade.

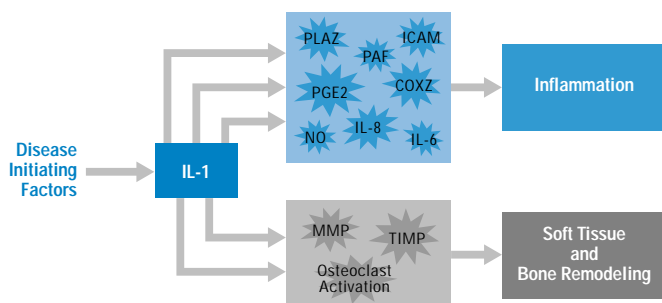


Figure 5. Biochemical cascade.

In some studies, patients with IL-1 gene variations had 2-4 times higher levels of IL-1, as measured in GCF and gingival tissue, compared to patients without these variations. In one study, some individuals positive for these IL-1 gene variations demonstrated extensive bone loss in their 40's, but comparable disease was not evident in subjects without these variations until after age 60. In a subsequent study by Mc Devitt and co-workers, over 60% of the patients with severe bone loss ≥ 2.5 mm were IL-1 genotype positive. Socransky and co-workers reported over triple the percentage of IL-1 genotype positive subjects exceeding the various mean attachment level thresholds than those negative for the genotype. The bottom line is that severe generalized disease is a rate problem (Figure 6). Some patients just seem to be on

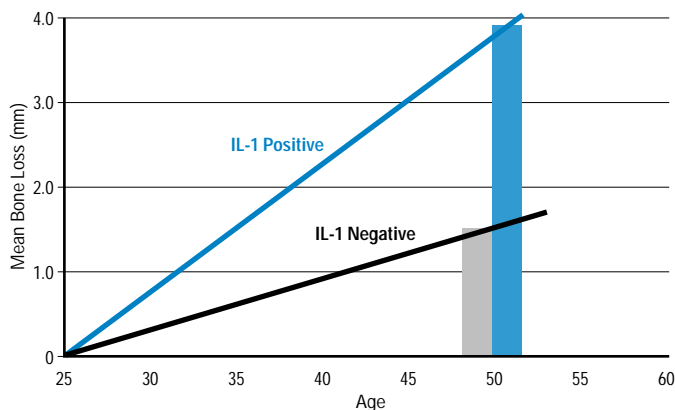


Figure 6. Severe generalized disease is a rate problem.

a different path when the bacteria are not adequately controlled. We now have evidence that the disease trajectory is influenced by genetics, smoking, and diabetes.

It has also been demonstrated that these IL-1 variations alter the response to therapy as evaluated in long-term maintenance populations. Lang, Tonetti and co-workers have reported that IL-1 genotype positive non-smoking maintenance patients are less likely to show improvement than their genotype negative counterparts. McGuire and Nunn demonstrated that smoking and positive IL-1 genotype predict tooth loss after periodontal therapy both independently (approximately 3x for each) and combined reporting a 7.7 times greater likelihood. This is indicative of a synergistic interaction between smoking and a positive IL-1 genotype. In addition, IL-1 genotype positive patients have been shown to have a less favorable response to regenerative therapy between one and four years postoperatively. Almost 80% of the IL-1 genotype positive patients lost ≥ 2 mm of new attachment during this period.

In addition to the IL-1 genotype, there have also been other risk factors that influence the progression of disease. It has become very clear in recent years that smoking and diabetes are significant risk factors for more severe periodontitis and for a less predictable response to therapy. With ongoing research we will better understand how these risk factors interact with each other and if they do indeed produce multiplicative effects.

Furthermore, it is important to emphasize that chronic diseases such as periodontitis involve complex biological interactions over time. The relationship between the IL-1 gene expression and a few single nucleotide polymorphisms (SNPs) describes only one dimension of the biology involved. On a clinical level the actual expression of IL-1 in a specific site in a specific patient undoubtedly involves complex interactions among local and systemic factors.

How does this risk information alter treatment decisions?

Now we must come back to how this information affects management of patients. Treatment decisions have primarily been based on an evaluation of past destruction of the disease and our historical perspective that periodontal therapy “works” on the vast majority of patients. Now we have a tool at hand that allows us to better identify prior to treatment that group of patients that continue on a trajectory toward severe disease. This tool is risk assessment. Treatment decisions can be made incorporating both what we know about the past anatomical destruction and the risk for future progression. Risk assessment offers the opportunity for more comprehensive disease management for those individuals identified at higher risk.

Similar to what we learned from McGuire’s prognoses papers, we are highly accurate with teeth that have a good prognosis but less than 50% accurate with anything less than good. Where do clinicians need the greatest help? What cases are the more problematic for the clinician? What cases incur the greatest morbidity and cost? Most of

us would say the moderate to poor prognostic cases where we previously have had few prognostic tools to accurately guide our treatment decisions. We know that about 80% of our patients respond very well to periodontal therapy exhibiting minimal progression and tooth loss. However, we also know that the remaining 20% experience moderate to severe progression with substantial tooth loss despite our therapeutic efforts. Insurance companies further reinforce this point indicating that the greatest utilization of dental services and cost expenditures result from 20-30% of the insured population. Our prospective ability to identify and target our efforts at this subset of patients who are more problematic, but most likely to benefit from intensive and comprehensive treatment efforts, will become increasingly

necessary to improve health while managing the burgeoning costs of healthcare. This may not be as overwhelming as we once thought. A small set of risk factors appears most dominant in predicting the future progression of periodontitis (Figure 7).

Interestingly, these factors are also risk factors for the progression of many other chronic diseases.

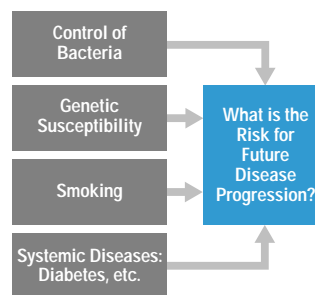


Figure 7. Risk for future disease progression.

What do you see as the logic for the IL-1 gene variations being associated with an exaggerated inflammatory response and are there implications for other systemic diseases?

First, the severity of periodontal disease varies substantially due to the different ways people respond to the challenges. Remember earlier, I said that severe generalized disease was primarily a rate problem. Figure 8 again depicts this point.

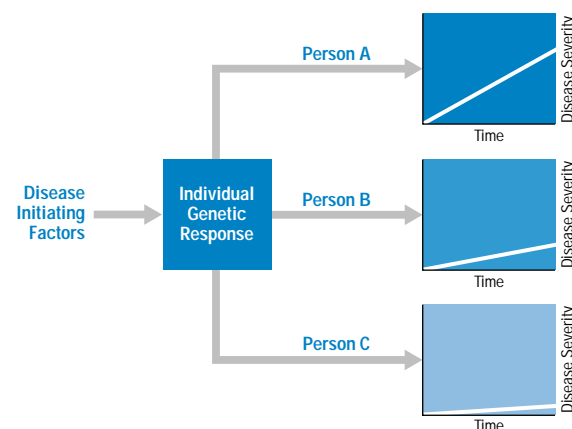


Figure 8. Severity determined by host response to challenge.

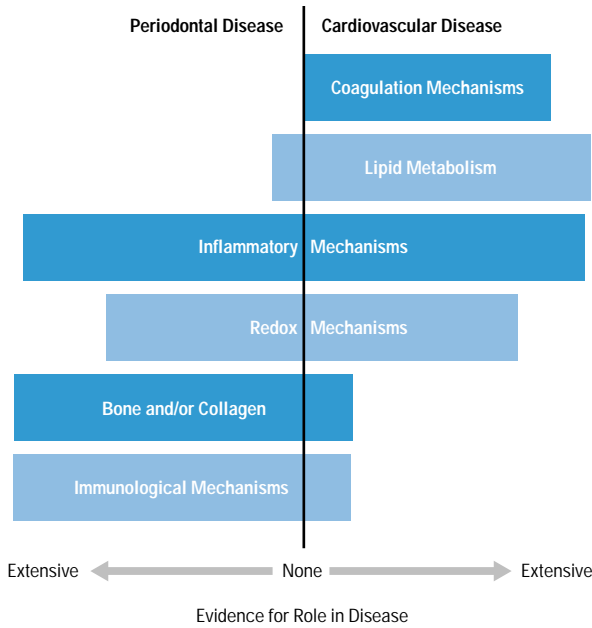


Figure 9. Biological mechanisms.

Secondly, common mechanisms mediate the body's response to multiple disease initiating factors through shared gene pathways. In the case of periodontitis the initiating factor is bacteria whereas for atherosclerosis the factor is cholesterol. Figure 9 qualitatively illustrates the amount of evidence supporting the role of certain biological mechanisms in both periodontitis and cardiovascular disease and what mechanisms overlap the two diseases. As is clear from this illustration, the strongest common denominators are the inflammatory mechanisms involved with both diseases. Nicklin and co-workers recently reported that severe inflammation developed around the large arteries in mice when IL-1 was over-expressed. Inflammation mediates tissue damage that translates into clinical consequences of disease. Increasing evidence continues to support the role of IL-1 as a high leverage system in many chronic inflammatory diseases/conditions.

What do you mean when you say IL-1 is a high leverage system?

Simply that

- IL-1 is a critical part of the body's response to disease challenges.
- IL-1 gene variations amplify the body's response to a disease challenge.
- IL-1 gene variations alter the disease pathway.

Therefore, IL-1 gene variations are risk factors for future disease progression. Risk assessment is disease management. Disease management alters treatment. I have tried to illustrate this logic in Figure 10.

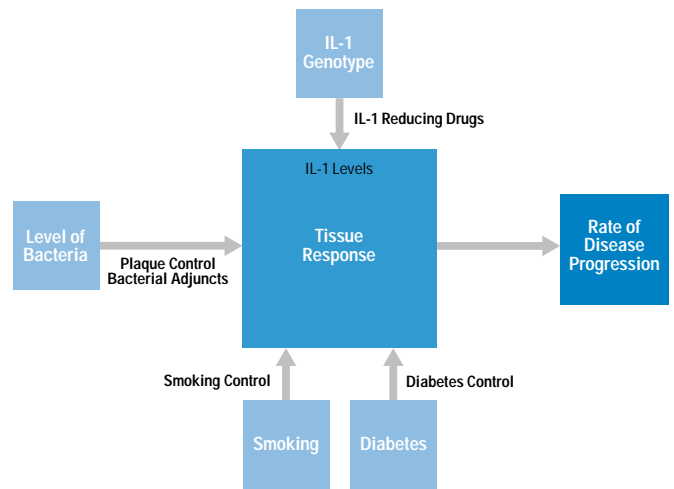


Figure 10. Disease management based on risk assessment.

Thank you.

Technical Update

What new evidence is available about the role of the IL-1 genotype and smoking in the treatment and progression of periodontal disease?

EVIDENCE SUMMARY:

1. IL-1 genotype positive periodontal patients who were also current smokers exhibited 5- 6 times the risk of tooth and bone loss as compared to genotype negative, non-smoking patients.
2. IL-1 genotype positive non-smoking subjects over age 50 and genotype positive smoking subjects showed greater mean pocket depths or a greater percentage of deeper (>3.5 mm) pockets than the genotype negative counterparts.
3. Statistically significant differences were shown in attachment loss and percentage of sites showing more than 6mm of attachment loss between the IL-1 genotype positive and genotype negative patients with periodontal disease.
4. Data from multiple independent studies reinforces greater tooth, bone or attachment loss in individuals who are IL-1 genotype positive.
5. Smoking and a positive IL-1 genotype have been shown to be synergistic risk factors further accelerating disease progression. As such, smokers may be prime candidates for PST testing.
6. Non-smoking, IL-1 genotype positive patients and smoking, genotype negative patients can be maintained comparably to non-smoking genotype negative patients with stringent compliance and aggressive supportive care.
7. Complete root coverage of mucogingival defects in healthy subjects was achieved in only 40% of the IL-1 genotype positive individuals as compared to 76% of the genotype negative subjects.

BACKGROUND:

The "first" landmark symposium dedicated to the importance of prognosis and risk factors in treating dental destruction and maintaining oral health was held at the University of Berne in May 2001. This symposium, *Risk Factors in Dentistry*, was a comprehensive review of the "state of the science" for how risk factors impact treatment decisions

and prognosis in dentistry today. A group of highly respected international speakers presented the current status of risk assessment in managing everything from dental caries to periodontal disease to dental implants. Lang and co-workers are to be congratulated on the success of this meeting and the significance it has for moving the profession forward.

At the symposium, Axelsson presented results from his most recent study investigating the impact of smoking and the IL-1 genotype on tooth and bone loss. This investigation was conducted in a well-controlled periodontal maintenance population with a randomized sample of 50 year-old Swedes who were comprehensively examined at baseline and followed longitudinally for a ten year period. The variables recorded included: number of teeth, alveolar bone level, probing attachment level, periodontal treatment needed as well as a detailed questionnaire to ascertain patient variables such as smoking status, oral hygiene habits, systemic disease and other lifestyle habits. At the ten year re-examination, the study population was given the PST test.

Axelsson highlighted preliminary results at this symposium. The study population consisted of 276 maintenance patients who were highly compliant with over 95% of the subjects receiving routine maintenance and additional needs-related therapy during the ten year period. As a result of this meticulous maintenance program, the overall average number of teeth lost was <0.4/subject for the follow-up period. This is impressive given that over 40% of the subjects (123/276) in this study tested positive for the IL-1 composite genotype. However, in order to better understand the impact of the **patient variables**, the subjects were then categorized by IL-1 genotype and smoking status into four evaluation groups: non-smokers/genotype negative (125/153), non-smokers/genotype positive (101/123), smoker/genotype negative (28/153) and smoker/genotype positive (22/123). In analyzing the data by these four groups, some important differences emerged. The **non-smoker/IL-1 genotype negative patients exhibited minimal progression** with an average tooth loss of 0.16/subject and alveolar bone loss of 0.26mm; whereas, the **smoker/genotype positive patients exhibited almost 6 times the tooth loss** with an average of 0.95/subject and over **4.5 times the bone loss** with a mean of 1.2mm/subject (Figure 11).

Analysis using frequency distributions looking at tooth and alveolar bone loss from 1988-1998 further substantiated the potential "synergy" between smoking and a positive IL-1 genotype. Figures 12 and 13 clearly demonstrate that even though the overall tooth loss was extremely low (<0.4/subject), certain individuals were definitely at higher risk for substantial loss of bone and teeth with almost **10% of**

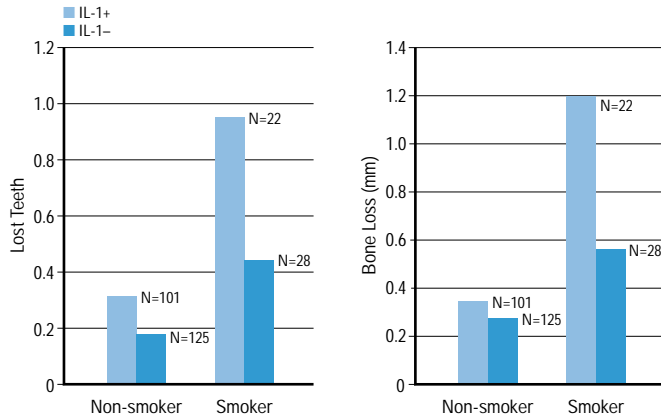


Figure 11. Lost teeth and alveolar bone loss by IL-1 genotype status and smoking.

the smoker/IL-1 genotype positive group losing more than 8 teeth and 25% experiencing greater than 1.2mm of bone loss.(1)

These findings confirm previous reports of greater tooth or bone loss in individuals who are IL-1 genotype positive, especially when smoking is an added risk factor. Axelsson and co-workers expect to publish the final results in the near future.

Furthermore, these data complement previous work reported by Hirschfeld (1978), McFall (1982) and McLeod (1997) that concluded that about 80% of patients will experience minimal disease progression and tooth loss (average tooth loss= 0.5-1); whereas, 20% will experience more disease progression losing an average of at least 5 -14 teeth. (2,3,4)

Axelsson's results are also reinforced in another study recently presented by Cullinan and co-workers at the University of Brisbane. The aim of the study was to investigate the relationship between the IL-1 genotype and periodontitis in a prospective longitudinal study in an adult population of 295 subjects essentially of European heritage. Probing depths and relative attachment levels were recorded at baseline and over the course of the five year follow-up period. Periodontitis progression at a given site was defined as attachment loss \geq 2mm at

any observation visit. The extent of disease progression was then determined by the number of sites showing attachment loss. Almost 39% of the subjects were positive for the IL-1 genotype. A relationship was found between a positive IL-1 genotype and increased mean probing pocket depth in non-smokers over the age of 50. Furthermore, positive IL-1 genotype smokers and genotype positive subjects with *P. gingivalis* in their plaque had an increased number of probing depths \geq 3.5mm. There was a consistent trend for IL-1 genotype positive subjects, especially smokers, to experience more attachment loss when compared with genotype negative subjects. (5)

Recently published data from Papapanou and co-workers adds to the mounting evidence regarding the value of the IL-1 genotype in association with disease progression. Papapanou evaluated 205 subjects (132 periodontal patients and 73 periodontally healthy individuals) for the effect of the IL-1 gene variation and periodontal status as

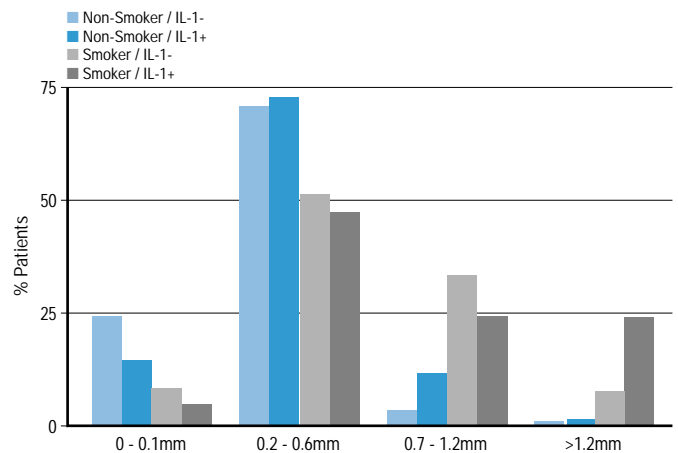


Figure 13. Alveolar bone loss, 1988-1998.

determined by clinical, bacterial and serum antibody parameters in a case-controlled study design. Papapanou found **statistically significant differences between IL-1 genotype positive and negative subjects in attachment loss for both mean attachment loss and percentage of sites with >6mm loss in the periodontal disease test group including both non-smokers and smokers.** (6)

In addition, Papapanou's paper underscores an important point regarding the use of genetic risk factors. Since the IL-1 genotype does not cause the disease, it cannot reliably determine who will or will not get disease. As such, screening healthy patients with no family history of disease or signs of inflam-

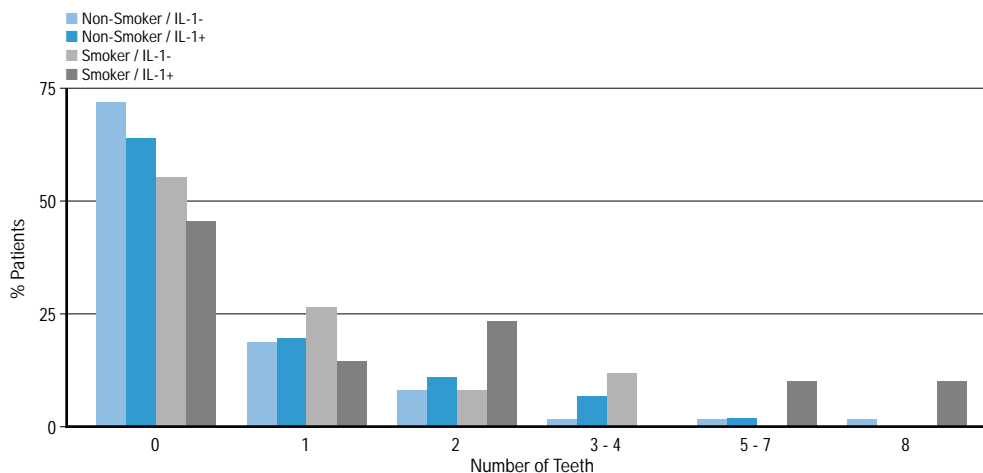


Figure 12. Frequency distribution of lost teeth, 1988-1998.

mation may not be of high value. Equally important, his data clearly demonstrates that once disease is present, the IL-1 genotype information is associated with disease progression and therefore contributes important information for predicting future progression and facilitating the ongoing management of the disease.

Cattabriga and co-workers recently published their findings on the influence of the IL-1 genotype on radiographic bone levels in a periodontal maintenance population followed for ten years. Sixty non-smoking patients were included in this evaluation of which 23 were determined to be IL-1 genotype positive (38.3%). On average, the results indicated no significant differences in tooth loss, 2.9% for IL-1 genotype negative and 3.9% for genotype positive. In addition, no significant differences were observed between IL-1 genotype negative and positive patients for mean changes in bone defect and bone crest levels. However, by looking only at averages, dramatic individual differences can often be overlooked. With that in mind, these investigators observed, on an individual patient basis, notable differences in response to therapy depending on initial bone levels and IL-1 genotype. They concluded this could be of value in predicting treatment response variations. (7) Again, these results closely relate to those of Axelsson, and **confirm if the patient is meticulously maintained and highly compliant there are no differences in treatment outcomes between IL-1 genotype negative and positive non-smoking patients.** Being genetically susceptible does not doom the patient to lose teeth.

Caffesse and co-workers reported similar conclusions in evaluating the effect of the IL-1 genotype on a healthy Hispanic population treated for mucogingival surgery. In this study on 22 patients, the authors concluded that the average result in covering localized gingival recessions is similar and periodontal health could be maintained with proper preventive maintenance irrespective of the genotype. However, an important observation in this study is the substantial difference in the amount of the root coverage depending on IL-1 genotype. Almost double the number of patients who were IL-1 genotype negative achieved full coverage of the mucogingival defect, 76% (13/17) as opposed to 40% (2/5). (8) Given the important role IL-1 plays in the inflammatory process and how critical inflammation is to wound healing, this observation suggests that additional wound healing research is warranted.

Can inhibition of the hyperinflammatory response prevent or slow periodontal destruction in IL-1 genotype positive patients?

EVIDENCE SUMMARY:

1. **Significantly elevated levels of IL-1 α were measured in medically healthy subjects with a positive IL-1 genotype.**
2. **IL-1 α levels were 4 times as much in non-smoking periodontal patients with the IL-1A, allele 2, polymorphism**
3. **Inhibition of IL-1 and TNF can significantly decrease the**

amount of periodontal destruction by at least 50% and as much as 90%.

4. **Inhibition IL-1 and TNF prevented bone loss in both menopause and arthritis. Both have a substantial inflammatory component.**
5. **Reduction of IL-1 can positively impact the risk and trajectory of diseases in individuals with a hyperinflammatory genotype.**

BACKGROUND:

Increasingly, there is evidence supporting the hypothesis that various combinations of alleles on the IL-1 genes differ in the way they produce the IL-1 cytokine, even in otherwise "healthy" individuals. Hukkonen and co-workers recently reported that **significantly elevated levels of IL-1 α were detected with the homozygous IL-1A (2,2) polymorphism and this effect was even more pronounced in the healthy donors who also were carriers of the IL-1B allele 2.** The authors concluded that these data suggest that this allele combination has a regulatory effect on basal IL-1 production. (9) Another study by Shirodaria and co-workers evaluated IL-1 α protein levels in periodontal patients. Results showed that allele "2" present in the IL-1A gene was associated with a **4-fold increase in IL-1 α protein levels** in GCF for the diseased non-smoking population. The authors concluded that this data suggests the allele 2 polymorphism modulates the production of IL-1 α thereby influencing the pathogenesis of the disease. (10)

The relationship between IL-1 levels and loss of tissue has also been the focus of several recent publications. Delima and co-workers reported that **IL-1 and TNF inhibitors significantly reduced the loss of attachment by 51% and loss of alveolar bone height by 91%**, concluding that inhibition of IL-1 and TNF may provide an important treatment modality to minimize the tissue destruction resulting from disease. (11) Similarly, Assuma and co-workers reported that despite a heavy bacterial challenge, the group with blocked IL-1 and TNF α exhibited a 67% reduction in osteoclasts and a **60% reduction in bone loss** in a monkey periodontitis model. (12) Requirand and co-workers reported on the correlation between lower levels of omega-3 fatty acids (an IL-1 inhibitor) and more severe bone loss in periodontal disease. (13)

Recent IL-1 studies involving other conditions such as arthritis and menopause have compared bone loss to IL-1 levels and reported a direct "cause and effect" relationship. For both, the higher the IL-1 level present, the greater the bone loss. Conversely, blocking production of IL-1 and TNF resulted in no loss of bone. (14,15,16)

Reduction of IL-1 decreases inflammation and the risk for periodontal disease progression. This knowledge, combined with our ability to identify individuals with exaggerated inflammatory responses, should provide additional avenues for treatment.

What is the impact of the IL-1 genotype and smoking on dental implant treatment and prognosis?

EVIDENCE SUMMARY:

1. In non-smoking, well-maintained patients, there is no statistically significant correlation between a positive IL-1 genotype and long-term implant failure or complications.
2. Preliminary data suggests a “synergy” between smoking and a positive IL-1 genotype impacting implant failures, complications and bone loss progression.
3. The prevalence of positive IL-1 genotype individuals in implant maintenance populations corresponds to prevalences previously reported for ethnic groups of European descent in periodontal maintenance populations.
4. Supportive care programs and implant “warranties” could now be differentiated on the basis of IL-1 genotype and smoking.
5. Smokers contemplating dental implant therapy may be a priority indication for PST testing.

BACKGROUND:

Buser and Gruica from the School of Dental Medicine, University of Berne recently reported on the roles the IL-1 genotype and smoking play in implant failures and complications. They evaluated 180 patients between the ages of 25 and 90 from Buser’s long-term dental implant maintenance population who had one or more ITI implants. All implants had been in function for at least eight years, with the range being 8 -15 years. The study population consisted of 51 implant failures or biologic complications in 34 patients and 241 surviving implants without any complications in 146 patients. A biologic implant complication was defined as suppuration in the periimplant sulcus, bone loss, a fistula or periimplantitis with radiographic bone loss. Of the 180 patients, 53 were smokers and 127 were non-smokers. Given the reluctance of many clinicians to place dental implants in smokers, Buser and Gruica thought it important to evaluate both smoking and non-smoking patients in this study. All patients were evaluated for the IL-1 genotype in the spring of 2001.

Buser presented their preliminary findings at the symposium *Risk Factors in Dentistry* at the University of Berne in May 2001. Sixty-four of 180 (36%) subjects tested positive for the IL-1 genotype. This prevalence corresponds to previous reports in populations of European descent. In certain respects, their findings substantiated previous reports by Wilson (1999) and Siervo (2001). Both of these investigators found, in their predominantly non-smoking study populations, no correlation between dental implant failures and a positive IL-1 genotype. Likewise, preliminary findings in the Buser and Gruica study indicated no significant correlation between implant failures/complications and a positive IL-1 genotype for the non-smoking group.

However, the fascinating finding emerging from this study was the strong interaction between smoking and a positive IL-1 genotype. Similar to results reported by Axelsson for tooth loss, there was a clear association between smoking and a positive IL-1 genotype with implant failures/complications. Buser reported that 50% (6 /12) of the patients that were heavy smokers and IL-1 genotype positive had either an implant failure or complication during the follow-up period (Figure 14). (17) This finding has led the investigators to the preliminary conclusion that there is a **strong, synergistic effect, between positive IL-1 genotype and smoking that puts implants at a significantly higher risk to develop a biologic complication.**

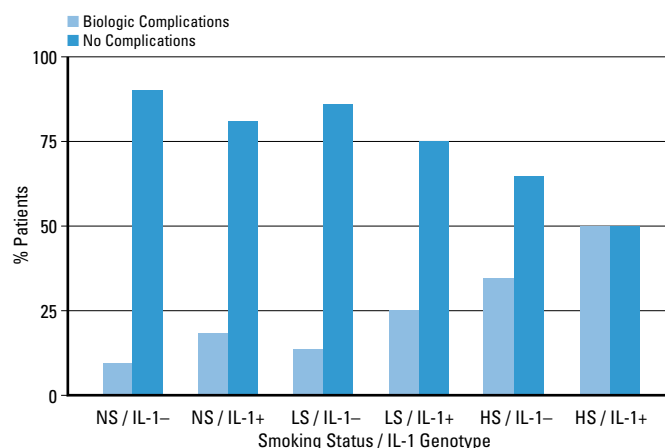


Figure 14. Complications by IL-1 genotype and smoking status.

Recently, Lang also completed a study looking at the association between a positive IL-1 genotype and dental implant complications in both non-smokers and smokers. He evaluated bone loss progression for surviving and failed implants. **Preliminary results indicate that smokers with a positive IL-1 genotype are at greater risk for more severe bone loss around implants.** Both the total as well as the per annum bone loss rates were significantly greater in IL-1 genotype positive smokers as compared to the IL-1 genotype negative smokers. Similar to the tooth loss findings, no significant differences could be detected in non-smokers between IL-1 genotype positive and negative subjects. Once again, this seems to be a trend in well-maintained populations. (18)

With the completion of these studies, the investigators are now looking for ways to apply this new evidence in the clinic. Given the high cost and patient commitment involved with major implant reconstructions, clinicians are often faced with the expectation of an implicit “warranty” should the procedure fail. If complications develop, the clinician usually manages these with no additional cost to the patient. However, by making this warranty explicit, the clinic at Berne is hoping to be able to share and discuss both clinician and patient responsibilities more proactively. To this end, they are taking a programmatic approach with an “Implant Warranty Program”. In this program, both **patient compliance and risk are factored into the patient’s expectations for success.** As presented by Buser, the essence of

this program is to tailor the recall program and patient compliance commitments so that they are in alignment with the two major risk factors, a positive IL-1 genotype and smoking. This means for non-smoking/IL-1 genotype negative patients, the follow-up program can be effectively reduced, making compliance easier for the patient without compromising the treatment outcome. For non-smoking/IL-1 genotype positive patients and smoking/IL-1 genotype negative patients, they will continue with the same recall and compliance program already in place at the clinic, since the results reinforce that this is sufficiently aggressive to maintain those patients and their implants. However, **for the smoking/IL-1 genotype positive patients, they will not offer a “warranty” at all, unless the patient successfully completes a smoking cessation program and/or agrees to a much more aggressive recall and compliance program.**

Siervo and co-workers recently published their findings on the association of the IL-1 genotype and implant failure in their implant maintenance population. The study population included 16 patients with 24 failed implants and 37 randomly selected patients with 39 functioning implants. The implant failures ranged from at least 1-7 years post-loading. All 53 patients were evaluated for the IL-1 genotype and bio-corrosion of the implant suprastructure. Seventeen of the 53 (32%) patients tested positive for the IL-1 genotype with 3 of 16 (19%) in the failed implant group as compared to 14 of 37 (38%) in the implant survival group. **This study, in predominantly non-smokers, found no association between late stage implant failures and a positive IL-1 genotype.** (19) However, it is interesting to note that of the three IL-1 genotype positive patients in the failure group, two were current smokers and of those two, one patient lost four implants.

Finally, Wilson and co-workers, in a multi-center study designed to evaluate the impact of the IL-1 genotype in late stage implant failures, has tested approximately 75 failed implants and 75 surviving implants for the IL-1 genotype. This is an international multi-center evaluation including both smokers and non-smokers. Based on a personal communication, the preliminary findings from this practice-based evaluation are complementary to the data emerging from the University of Berne. (20)

Today smoking is well accepted as an important risk factor in dental implant therapy. As a result, many clinicians are reluctant to treat smokers with implants especially in combination with complex procedures such as bone grafts or sinus elevations. However, this emerging evidence suggests it may be possible to identify and treat some smokers with a higher degree of confidence. In other words, **smoking patients who are IL-1 genotype negative may be effectively treated and maintained with dental implants using the current standard approach.** This is also true for those non-smoking patients that are IL-1 genotype positive. It is the combination of these two risk factors that appears to negatively impact the prognosis for implant survival.

What are the primary clinical applications for the PST Test?

Abundant evidence has emerged since the original publication in 1997 showing an association between a positive IL-1 genotype and risk for severe periodontal disease. At least fifty new publications combined with the clinical experience of leading clinicians throughout the world have helped to clarify where the PST test has potential clinical value. These applications are summarized as follows.

- 1. Current and recent smokers to support smoking cessation and more aggressive supportive care in:**
 - a. Preparing for treatment
 - b. Periodontal maintenance programs
 - c. Dental implant maintenance programs
- 2. Cases with a questionable prognosis to influence the treatment plan for:**
 - a. Complex restorations
 - b. Severely compromised teeth
 - c. Non-responders to treatment
- 3. Patients with early signs of disease to assess risk and disease trajectory, who exhibit:**
 - a. Generalized BOP
 - b. Radiographic bone loss
- 4. Patients contemplating extensive and expensive procedures to set realistic expectations and influence case management for:**
 - a. Major periodontal surgery
 - b. Dental implant treatment
 - c. Orthodontic movement
 - d. Mucogingival surgery
- 5. Patients with pre-existing conditions or at high risk for medical complications to better manage their periodontal disease and positively impacting overall health for:**
 - a. Diabetes
 - b. Cardiovascular disease
 - c. Osteoporosis
 - d. Respiratory diseases
- 6. Female patients with periodontal disease to determine risk for pregnancy complications who are:**
 - a. Presently pregnant
 - b. Contemplating pregnancy
- 7. Family members, to determine if susceptibility has been inherited, of patients:**
 - a. With severe periodontal disease
 - b. Who tested positive for the IL-1 genotype

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