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Contemporary approaches for identifying individual risk for periodontitis

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Running title: Individual Risk for Periodontitis

WHY do we need to individualize periodontal care?

Beginning in the late 1960's and extending through the mid-1980's, several impressive clinical studies successfully simplified the causation of gingivitis and periodontitis to establish a primary role for bacterial accumulations on the teeth. (57, 72, 73, 94) These early studies focused on initiation and reversal of gingivitis and demonstrated that the basic concept of a critical role for bacterial accumulations in periodontitis held up in dogs and appeared to be similar in populations such as tea workers in Sri Lanka.(65, 66, 71)

[Figure 1 Here]

The key observations of a primary "cause" of gingivitis and periodontitis were followed by landmark longitudinal studies at the University of Michigan and the University of Gothenburg which established core principles in prevention and treatment of periodontitis.

The clinical experimental gingivitis studies in dental students and the experimental periodontitis studies in dogs strongly supported the general concept that bacterial accumulations on the teeth predictably led to gingivitis and if untreated progressed to periodontitis. The details of some of those studies and observations by many clinicians did not however support the concept that periodontitis was a simple linear relationship between bacterial accumulations and initiation and severity of periodontal disease. In spite of important gaps or contradictions in the evidence, the basic message was that we could predictably prevent and treat periodontitis by a combination of professional and patient-directed approaches to bacterial control. That was a major advance over the clinical concepts in the preceding period that resulted in conflicting approaches to treatment of periodontitis, and therefore less predictability in outcomes.

Unfortunately, we communicated to many dentists, hygienists, and patients an implicit extension of the new concept that suggested the severity of periodontitis was a simple function of the magnitude of bacterial accumulations and the time of exposure. The unspoken corollary was that given a bacterial exposure all individuals are equally susceptible to periodontitis, and if treated using the proven principles from the longitudinal studies patients should respond in a predictable manner. If those concepts are correct, there is no clear value to stratifying a patient's risk for developing periodontitis or responding predictably to therapy.

Evidence indicates some individuals have greater risk for developing severe periodontitis and some do not respond predictably to standard treatment principles and maintenance care.

Two major exceptions emerged but failed to dissuade clinicians from the concepts that everyone was equally susceptible and that everyone responded predictably to bacterial reduction therapy. The first exception was that among populations with no routine oral hygiene or professional dental care, most individuals developed only mild to localized moderate periodontitis.(6, 70) The evidence that emerged from Sri Lanka over time indicated that despite extended exposure to substantial levels of bacteria and calculus on the teeth, only a small percentage progressed to severe generalized periodontitis.

[FIGURE 2 Here]

The second exception was that among patients treated and maintained appropriately for advanced periodontitis, approximately 20 to 25% continued to have disease progression and lose teeth,(41, 68, 76) and in some studies the disease progression during post-treatment maintenance care was associated with a small number of patient-level risk factors.(22, 61, 62, 77, 102, 104)

In addition, when adults, most of whom had participated in a standardized prevention program, were reevaluated after 10 years, 12.3% of the patients had lost multiple teeth due to periodontitis.(98) Recent studies of various designs appear to support earlier observations that some individuals, based on specific risk factors, have an increased risk for severe periodontitis or for increased tooth loss or periodontitis progression.(25, 33, 34, 79, 80, 119) Those studies and observations by many clinical periodontists are the primary rationale for individualizing risk for periodontitis.

Chronic complex diseases have variable presentations among affected patients and most likely reflect the cumulative biological result of multiple factors that modify various components of the pathophysiology of the disease. Progressive tooth loss in a subset of patients treated for

periodontitis is consistent with general concepts of the clinically meaningful role of individual differences in chronic diseases

It is all about prevention of severe disease and complications? Leroy Hood's "P4 Medicine" has succinctly captured not only the overall vision of precision healthcare but emphasizes the critical role of prevention in precision medicine as an essential strategy for controlling chronic diseases.(28, 43, 44)

P4 medicine refers to programs that are:

- **Personalized.** Identifying on which disease path an individual is traveling as they age.
- **Predictive.** Identifying the disease path before an individual has developed a severe form of the disease or a major complication of the disease
- **Preventive.** If one can intervene early at the predictive stage to modify the disease path there is an opportunity to extend the time until which the individual develops sufficient disease severity and complications that there is compression of the individual's morbidity
- **Participatory.** Many chronic diseases require patient participation to best manage the disease. Both prevention and treatment of periodontitis have a participatory element that is substantial, if not deterministic.

No facts about the future, only probabilities: Risk factors are how we estimate an individual's probability for future disease progression and response to standard therapies

What do we mean by "individual risk for periodontitis"?

Physicians and dentists have long used personalized approaches to manage their patients. The new era of precision medicine, often referred to as personalized, individualized, or stratified medicine, attempts to take advantage of molecular signatures or individual biomarkers combined with traditional risk factors to better predict the course of one's disease or to guide choice of therapies.

Clinical use of precision medicine in oncology and rare disorders have greatly benefited patients through new drug development and better drug outcomes. For example, there are two main histologic subtypes of lung cancer which result in more than 150,000 deaths annually in the United States. In the past 10

years subsets of non-small cell lung cancer have been identified based on mutations in key control points of multiple oncogenes. Of the current 15 gene mutations that have been identified, drugs are currently approved for 8 of the 15.(114) At the moment, much of the focus in oncology is on matching the right drug to the causative mutation to stop disease progression and increase survival.

Use of precision medicine in oncology and rare diseases is a valuable model but does not translate well for chronic diseases. In chronic diseases many of the strongest risk factors are environmental or acquired factors, such as smoking, diet, and obesity. The clinical features of a chronic disease phenotype are often the result of multiple biological pathways, each of which includes multiple genes and environmental factors that interact to regulate the pathway and ultimately the clinically observable expression of disease. For common chronic diseases, the biology is not as deterministic as in oncology and rare diseases, and the clinical expression is a probabilistic summation of the key pathways and their components.(63) The net result of the complexity of chronic disease is not 8 or 15 molecular subtypes of the disease that define treatment choice and response, as in non-small cell lung cancer, but rather a small number of clinical disease patterns that represent different trajectories over time and different responsiveness to standard interventions.

These are likely the result of many molecular subtypes that produce a few clinical disease patterns, or phenotypes. Individuals with observed variations in clinical presentation, including age of onset, severity and extent of disease relative to age, and predictability of clinical response to conventional periodontal therapy, are unlikely to have differences in the actual pathophysiology of periodontitis in the periodontal tissues.

One might conclude that the functional changes in disease-associated tissues compared to health-associated tissues represent basically the same pathophysiology, regardless of the clinical differences among patients. If that is the case, then individuals with variations in clinical disease likely have the same disease. So, how do we explain the clinical differences we see? Based on current knowledge, individual differences in periodontitis progression appear to be explainable by biological modifiers including: environmental factors, such as smoking; genetic variations that modify the immune-inflammatory response, alter wound healing, influence bone and connective tissue remodeling; or an acquired disease such as uncontrolled type 2 diabetes, that influence the individual's host response to bacterial challenge. The net result of one or more of these modifiers is a change in the rate of certain physiological pathways to influence the biological response to the bacterial challenge and reduction of that challenge.

The chronic diseases often display disease heterogeneity,(107, 120) meaning that different pathways can lead to the same clinical phenotype, i.e. “many to one”, and also genetic heterogeneity, where one node in a pathway may lead to multiple diseases,(11) i.e. “one to many.” The latter phenomenon is evident when the same drug, e.g. a tumor necrosis factor-α blocker, shows clinical value with multiple complex chronic diseases.

To address the question of whether it is possible to identify individual risk for periodontitis, and perhaps more importantly is it practical to do so, one must start with a set of risk factors that have been individually validated. Since those risk factors likely influence one or more pathways, and we have multiple risk factors for a chronic disease such as severe chronic periodontitis, we must also have a mechanism to stratify patients using combinations of multiple risk factors.

This involves a long and demanding process that requires three successive steps: 1) identify/discover potential risk factors, 2) clinically validate putative risk factors, and 3) demonstrate clinical utility attributable to use of specific risk factors. Since the primary objective of this paper is to address the clinical utility question of whether we can currently identify individual risk for periodontitis, it is out of the scope of this paper to review the evidence for discovery and clinical validation of potential risk factors. Fortunately, there are outstanding recent reviews of the evidence for the major risk factors for periodontitis, (18, 32, 46, 52, 75, 118) and I will accept some of those factors as a starting point for this discussion of can we use existing clinical utility evidence, albeit very limited, to identify individual risk for periodontitis?

Identifying individual risk for periodontitis: Start by explicitly defining the Goal

1. *Risk for this patient developing periodontitis?*
2. *Risk for this patient’s periodontitis progressing to moderate to severe generalized periodontitis?*
3. *Risk for this patient having a less predictable response to standard periodontal therapies and maintenance care?*
4. *Risk for this patient’s periodontitis having implications for systemic disease?*

Step 1: Discovery of potential risk factors for periodontitis. Can we identify specific factors that are associated with patient differences in clinical signs of periodontitis, progression or severity, response to treatment, or systemic implications or periodontitis?

Step 2: Validity

Analytical validity refers to the accuracy with which a trait can be identified and quantified. This can refer to clinical parameters and the reproducibility of measurements among different clinical examiners or the same examiner over time. It is important to assure and make publicly available the analytical validity of biochemical, genetic, and physiologic assays, whether as single analyte assays or large multiplexed assays for which very different levels of expertise may exist across multiple laboratories and diverse assay systems. Analytical validity also includes validation of data management systems that are used to collect, analyze, and report data. In recent years analytical validity problems with -omics data have been reported as a result of failure to assure analytical and clinical validity prior to clinical application of gene expression patterns.(1, 78)

Clinical validity describes the accuracy of a specific risk factor to truly influence a particular clinical outcome. For example, is there evidence that a specific risk factor changes the biology in a manner that is relevant to severity/progression of periodontitis? Is the risk factor consistently associated with chronic periodontitis severity or progression?

A risk factor is often defined from an epidemiological perspective as an exposure that is associated with a particular clinical outcome(88), whether or not the relationship is causal. Since periodontitis initiation or progression must be observed over many years, clinical validity is often based on multiple confirming association studies. Randomized controlled intervention studies directed at modifying a specific risk factor provide the most convincing evidence of a risk factor's causality, but those are difficult to do in periodontal disease, and few exist. Fortunately, there are well-described criteria for assessing the likelihood of causality of a disease associated risk factor.(40) The criteria for clinical validity of risk factors in periodontal disease must start with consistent association of the factor with well-defined periodontal outcomes in appropriate populations. For some clinical uses we may be happy to have a marker that helps predict a maintenance patient's future likelihood of progression without concern whether the marker is causal, for example a certain level of bleeding on probing at multiple visits is a very good predictor of future progression even though bleeding itself is not causing the progression.(58, 59)

However, risk factors that are "causal" provide an opportunity to target the risk factor to prevent or treat disease. Given consistent associations of a risk factor with a periodontitis phenotype, one's confidence in the causality of the factor increases based on the following: 1) biological plausibility, 2) biological gradient or dose-response relationship, 3) temporal relationship; i.e. does exposure to putative causal factor precede disease phenotype, and 4) experimental evidence that tests a causal relationship hypothesis.(40) A risk factor with a consistent association and evidence to support causality, is more likely to influence a particular clinical outcome.

Since most individuals exposed to bacterial accumulations on proximal surfaces of the teeth for long periods of time will develop mild periodontitis with a few localized sites of moderate periodontitis, the primary importance of risk factors and individual risk for periodontitis relates to a more severe phenotype. Individual risk for periodontitis is important for patients who are more likely to: a) demonstrate generalized progression of or develop moderate to severe generalized periodontitis, b) exhibit clinical progression in the face of standard periodontal therapy and maintenance, and c) influence systemic diseases.

Risk factor clinical utility for a complex chronic disease such as periodontitis: Individualizing risk generally requires multiple risk factors and a way to integrate the influence of multiple risk factors in a single individual

Clinical utility refers to the likelihood that information about a specific risk factor or set of risk factors will lead to actions that improve health outcomes.

Clinical utility requires the application of risk factors to classify individuals into discrete groups that guide disease prevention or intervention. Many factors with very strong association data may not make good classifiers(47, 69). Garcia and colleagues(30, 31) have provided excellent discussions of the limited predictive value for some powerful risk factors in multiple diseases, and they also illustrate the challenges of predicting risk for an individual patient, which of course is critical to clinical value. As noted by Garcia and colleagues, many risk factors must be included to predict the majority of risk for death attributable to coronary artery disease.(30, 31) Although an individual risk factor may not be impressive in prediction of the total population risk of a specific complex disease, some single risk factors, for

example blood cholesterol, have proven to be a very valuable risk factor to guide use of statins to low levels of low density lipoprotein-cholesterol, and thereby reduce cardiovascular disease events, including myocardial infarctions and deaths.

Although, many patients are at risk for cardiovascular events due to other risk factors, an initial set of risk factors can be used to guide treatment for an important segment of the at-risk population. Such an approach also adds value by determining residual risk remaining in some patients after treatment based on the strongest risk factors initially identified. For example, in a randomized controlled clinical trial of more than 15,000 overtly healthy adults with no prior history of cardiovascular disease and "normal" low density lipoprotein cholesterol levels (< 130 mg/dL), the risk factor of elevated systemic inflammation (> 2 mg/L C-reactive protein) was used to target individuals who might benefit from high dose statins that modestly reduce systemic inflammation. This was an effective strategy, and demonstrated that high dose statins lowered even "health-associated" levels of low density lipoprotein cholesterol and inflammation to prevent first cardiovascular events, achieving a 54 percent heart attack risk reduction, based on actual reduction of clinical events compared to placebo.(106) In that intervention study based on successfully reducing the two strongest risk factors for cardiovascular events, a third level risk factor, lipoprotein(a) was identified as a residual risk factor that, in spite of lowering already low levels of low density lipoprotein-cholesterol and systemic inflammation, this patient group needed a different therapeutic approach now identified by a third risk factor. Multiple new drugs are in late stage development targeting the third risk factor, lipoprotein(a).(117)

In periodontitis, there are few studies that have been explicitly designed to test the hypothesis that risk stratification with specific factors, such as smoking, type 2 diabetes, obesity, genetics, or others, influence periodontal outcomes of therapy or preventive care.(33, 35, 91, 113) If biases are properly considered and adequate sample sizes are available, it is possible in some situations to use large retrospective databases to ask prospective questions relative to the influence of patient stratification on disease prevention or treatment outcomes. This "prospective-retrospective" study design is being used routinely in the effort to discover and validate biomarkers to guide the use of new drugs that are expensive and have the potential for serious adverse drug events. (97) The application of prospective-retrospective clinical trial designs in

Move risk factors to the clinical utility stage as early as possible. With common but complex chronic diseases, our goal should be to improve clinical management of the disease. As the decision analysis gurus teach us, there are no facts about the future, only probabilities. Prospective pilot studies allow us

to unravel the relative importance of multiple factors in critical disease endpoints, such as disease progression and response to specific interventions.

What are the practical elements required to get to clinical value?

Clinical utility indicates that there is a difference in the disease that is sufficient to influence the disease progression/severity (and therefore tooth loss and replacement), response to treatment, and systemic implications. The key question to be studied for clinical utility therefore goes beyond a simple disease association. The clinical utility question often has three parts: a) if a specific patient is in one specific risk classification, and b) is treated with different well-defined approaches**,** what is the actual observed frequency of a specific outcome?

Individualized periodontal medicine starts with stratifying patients into specific buckets

Although individualized periodontal medicine suggests that an individual patient may have a unique biological fingerprint and therefore receive a unique therapy, that is not the reality in most of chronic diseases. Individualizing risk must begin with criteria that allow every patient to be stratified into discrete and non-overlapping categories (Fig. 3). Stratification is often a key part of the clinical utility phase, since it must build on learnings during the discovery phase. Risk factors that are highly significant during the discovery phase may not be informative in stratifying individuals for clinical purposes. (47, 69) Complex diseases do involve thousands of interacting factors that probably could define a unique phenotype for every individual. Biological pathways that influence a complex disease in a specific individual interact, but some nodes in a pathway are more important than others and have leverage to change the disease outcome.(63) As with most chronic diseases,(110) the evidence suggests that individuals with periodontitis follow a small number of clinical paths that describe progression and severity patterns in the population. Similarly for periodontitis patients treated using standard principles, 70-80% of patients respond predictably and favorably,(41, 76) with the others either not complying with regular maintenance care or being enriched with a small number of risk factors.(22, 61, 62, 77, 79, 80, 82, 102-104, 112)

[Figure 3 Here]

Stratification may be simple or complex.

Current regeneration technology offers impressive opportunities to enhance supporting periodontal tissues and prolong retention of teeth. Predictable and useful periodontal tissue regeneration requires stratification of patients and sites to provide the most effective long-term outcomes.(51) Such stratification may use simple or complex patterns. Many parameters that are highly significant predictors of outcomes in large case-control studies may not be good "classifiers."(47, 69) The important aspect of good classifiers for practical clinical use is that specific parameters can be used separately or combined into a well-defined pattern that classifies individual patients into distinct categories that are of clinical value.

Simple stratification: Recombinant human platelet-derived growth factor BB homodimer (*rhPDGF-BB*) may provide very good long-term regenerative success in certain sites and for certain patients. A group of clinical investigators reported good long-term advantages over the scaffold alone, but only for smokers.(86)

[Figure 4 Here]

Although single risk factors are unlikely to be highly informative in observational studies of complex diseases, it is not uncommon to see single risk factors stratify responses to therapy or influence progression of complex diseases. For example, in a clinical trial of 7,018 high risk cardiovascular disease patients randomized to the American Heart Association low fat diet or the Mediterranean Diet and followed for more than four years, a single genetic factor (TCF7L2) explained a three-fold increase in strokes for individuals on the low-fat diet.(15) In addition, the Mediterranean diet essentially eliminated all added risk for strokes attributable to the TCF7L2 genetic effect. Other studies have reported that single genes, unrelated to drug metabolism, can have a major effect on clinical outcomes of drug therapy for chronic diseases (10, 16). To demonstrate clinical value in patient stratification, we should try as much as possible to ask a question about disease progression over time or response to treatment over time in prospective studies.

Not only do questions of disease progression and response to treatment allow us to get close to clinical utility, we also avoid multiple challenges inherent to case-control studies of periodontal disease. Two of the major challenges of periodontitis in observational studies are; 1) extraction of 6 to 8 teeth can

convert a case of moderate to severe generalized periodontitis into a case of mild disease with 20 remaining teeth, and 2) there are multiple factors, such as smoking, that appear to influence the initiation and progression of periodontitis.(7, 27, 49) The first challenge produces an incorrect classification of the patient. If one is studying genetic factors in severe periodontitis, false positives may be present when a specific genetic factor is present but extractions have produced a patient classified as having mild periodontitis. The second challenge produces a dilution of the effect size of any single factor, i.e. "many roads lead to Rome," and the statistical management of multiple risk factors may mask their individual differences in terms of disease phenotype and biology.(52)

How can one possibly combine multiple risk factors to establish the net risk for a single individual?

In periodontal disease one of the biggest challenges is how to account for missing teeth in cross-sectional or case-control studies. Prior history of periodontitis is strongly associated with future risk. When there are multiple putative risk factors, one should start with a few classic risk factors, such as smoking and type 2 diabetes. Initial studies should demonstrate significant association between the core set of risk factors and sequentially add exploratory or novel risk factors to assess whether for a specific phenotype the exploratory risk factor adds value to classic risk factors in this disease. Perhaps most importantly some risk factors modify the effect of classic risk factors on the disease outcome.(80, 81, 112, 116)

Complex stratification

Practical application of a risk factor model that includes multiple risk factors is challenging but essential for clinical utility for two primary reasons: 1) it recognizes that for complex diseases there are multiple physiological pathways that can lead to disease. To focus on only one of those pathways may result in many false negatives, as other factors may lead to the same phenotype. 2) Multiple risk factors may be additive, and in some cases conditional. For example, the Framingham Risk Score estimates an individual's 10-year risk for developing diagnosable coronary artery disease. Translation of the score into risk depends on an age and gender-based algorithm that combines multiple factors such as total cholesterol, blood pressure, and smoking. One can input a range of values for the risk factors and quickly see that using a single factor accounts for a limited part of the total risk for someone of a specific age and gender.(17) In addition, some risk factors, such as lipoprotein(a), that have been determined to be

causal for coronary artery disease(115) do not appear to result in major cardiovascular disease events unless there is a second factor present that amplifies the inflammation.(116)

The Periodontal Risk Assessment system, as developed and described by Lang & Tonetti (60, 61, 102) and shown in Fig. 5, is one example of tools that integrate multiple risk factors in assessment of periodontitis. The Periodontal Risk Assessment system allows the identification of individuals who may be at risk for disease progression due to multiple known and unknown factors. The risk may or may not involve an interaction between risk factors, but one of the strengths of the system is that it acknowledges a broad range of risk factors without forcing the system to include all factors.

More complex interpretations of multiple risk factors in a prediction model of course depend on having a broad range of data that allows validation of the value of the tool for different patients in different scenarios.

[Figure 5 Here]

It is reasonable to use selected risk factors together in a simple additive model, i.e. a patient with any 2 risk factors is assumed to be at greater risk than a patient with 0 or 1 risk factor. Such models may use regression data to assign a quantitative magnitude of effect to each risk factor or risk factors can be assumed to be of equal effect. In simple multifactorial risk models, it is important to predefine the risk interpretation of different possible combinations.(33) If adequate databases are available with well-defined progression data or clinical event data, one may evaluate the impact of adding new risk factors to a standard risk model by means of calculating a "net reclassification index"(13, 14, 100) which determines whether the new risk factor changes the risk classification of specific individuals to a clinically meaningful extent.

For many years some investigators have studied multiple aspects of chronic periodontitis with increasing attention to biomarker clusters that stratify subsets of chronic periodontitis.(39, 83, 89, 90) Because complex chronic diseases by definition involve multiple genes and multiple environmental factors that interact with many permutations, theoretically we may all be uniquely different at the molecular level. The challenge becomes how to set the granularity to a level that is clinically meaningful. The challenge of translating the biological complexity into actionable targets has been addressed recently relative to

cardiovascular disease, where the use of loss- or gain-of-function mouse models has implicated dozens of molecular targets as major drivers of atherosclerotic cardiovascular disease, yet few of these targets have been shown to be causal and have shown value in preventing or treating clinical disease.(63)

The challenges are how to move from single parameter discovery to the integration of multiple parameters and then to actual classification of individual humans. That is ultimately what we are asked to do when one changes the question from, “what are the major risk factors for periodontitis?” to “How can we identify an individual’s risk for progression or severity of chronic periodontitis?”

In recent years some groups (33, 90) have explored various approaches to stratifying individuals relative to chronic periodontal disease. As they and others experienced, biological explorations of chronic periodontitis using -omics approaches have not been greatly rewarding, perhaps in large part due to inherent weaknesses of periodontal observational databases for which a single phenotype is assumed.

Dr. Offenbacher and his colleagues used a large cross sectional database with periodontal data to identify a set of complex traits based on prespecified parameters, such as microbial patterns defined by eight periodontal bacterial pathogens and the status of periodontal inflammatory response as measured by interleukin-1β levels in gingival crevicular fluid.(92) Six patterns were identified based on two biological characteristics, markers of specific microbial ecologies and periodontal levels of inflammation. These six biologically defined patterns allowed each patient in the database to be matched to one of the specific patterns. The team could then explore genetic differences among the six biologically defined complex traits. This approach has multiple important advantages, including 1) the biology defined by a pattern has a narrowed search space relative to genetic influences, not unlike focusing on disease progression or response to treatment, and 2) every patient can be classified. Both of these study characteristics are important to advance towards clinical utility, because the starting point for studying the potential value of individualized risk for periodontitis is being able to classify every patient into a predefined category.

Offenbacher, Beck and colleagues have recently advanced the stratification to attempt to define clinical substructure in the disease to potentially untangle chronic periodontitis into multiple well-defined clinical classifications.(83) This again represents an important starting point to use the newly validated classifications to explore specific hypotheses about disease progression or different responses to periodontal therapy.

Using current evidence to individualize risk for periodontitis

The vast majority of individuals will develop periodontitis when exposed to an undisturbed subgingival bacterial mass over time. Observational studies indicate that most periodontitis will result in mild disease with a few local sites with moderate disease, regardless of the bacterial challenge.(6, 70) Evidence from interventional studies support a predictable periodontitis response to bacterial control in the majority of patients.(3-5, 41, 53, 54, 67, 68, 105) The opportunity as specialists is to identify subsets of patients who respond differently to a bacterial challenge and either express more severe periodontitis or do not respond predictably to standard clinical approaches to periodontitis prevention and treatment. For periodontists to act against these opportunities involves research to define how to stratify patients to identify those who require a different approach to clinical management, and to develop clinical protocols for efficient prevention d treatment of more complex cases.

Clinical Scenario 1: Primary Prevention of periodontitis at the population health level

If our goal is to reduce the prevalence of periodontitis among adults in a specific population, this is a population health initiative that is in part an access to care issue and an education issue. For example, in the U.S., epidemiological data indicate that periodontitis, and especially severe disease, is enriched in segments of the population below twice the federal poverty line. (24, 25) The same enrichment for severe periodontitis is seen in very targeted geographic locations in the U.S. that are dominated by lower socio-economic and education attainment.(23) A second population that is enriched for severe periodontitis, at least as represented by tooth loss, are individuals that have good access to dental care through employee-based dental insurance, but do not see the dentist regularly for preventive care.(33)

Using individual risk factor information to focus periodontitis prevention messages. Beyond educating mothers, children and young adults about the importance of oral hygiene and oral hygiene methods, we can start to focus the messages on individual risks for periodontitis. Some of the emphasis should be on the value of preventing periodontitis with the individual risk role that smoking and uncontrolled type 2 diabetes plays in periodontitis severity and complications of tooth loss. Although we are discussing a population health message, the approach can include self-awareness messages of individual risk, and the action message should encourage regular professional periodontal assessments to identify and

address periodontitis early and to educate about personal care. The individual risk message helps to personalize the risk and potential solutions for their individual needs.

Clinical Scenario 2: Use of individual risk for periodontitis to prevent moderate to severe periodontitis in individuals with access to dental care

Routine primary preventive care to reduce likelihood of periodontitis, as has been taught to dentists, hygienists, and patients for many years, is anchored by assumptions and expectations that are correct for the majority of our patients but fail to properly manage those who are at greatest risk. This has been shown to be true even for adult patients who have been managed by the well-proven "needs-related" approach to preventive dental care, as defined by Per Axelsson, Jan Lindhe, and others.(2, 99)

The current approach to primary preventive periodontal care in general dentistry includes two faulty assumptions and one incorrect expectation.

Two faulty assumptions:

1. the first faulty assumption is that all patients are equally susceptible to periodontitis, and the clinical expression of periodontitis results entirely from exposure to bacterial plaque over time.
2. the second faulty assumption is that periodontitis progresses slowly, so once a patient is identified with mild periodontitis, standard protocols will predictably manage the disease. The treatment approach generally used in such situations involves repeated prophylaxis with scaling and root planing as indicated in the isolated sites that show early periodontitis. Such approaches may be augmented with targeted interproximal oral hygiene instructions and local delivery antimicrobials.

There is also one incorrect expectation of the primary prevention outcomes described above, and that is that the patient with early mild periodontitis will respond predictably to the scaling and root planing of the sites with localized mild disease. The current standard in most dental offices throughout the world is that management of the initial scaling and root planing with first identification of mild periodontitis rarely has a follow-up to assess response of the patient. That of course is based on the reality that most patients will in fact respond very predictably to that therapeutic intervention.

Opportunities to add clinical value by individualizing risk for periodontitis

[Figure 6 Here]

The curves shown in Fig. 6 postulate what to expect in individuals who see a dentist regularly for routine preventive care. The question is what can we expect to see in terms of periodontitis progression to moderate to severe generalized periodontitis in patients who are part of the regular dental care system. There are large dental insurance databases, managed dental care databases, and nationwide epidemiology findings that can provide some insights to this question, but we must acknowledge the limitations. To some extent the boundaries of periodontitis expression may be seen in the studies of populations in Sri Lanka and Tanzania with minimal to no personal oral cleaning and no professional cleaning. (6, 70) Although not analogous to patients in routine dental care in the U.S., Europe, and Asia, the maximum disease boundary may be a good disease stratification perspective as one envisions applying such boundaries to individuals with access to routine dental care.

Most patients as shown in the blue line (Fig. 6) will have mild disease detected at some point and with appropriate preventive care will develop predominantly mild periodontitis with a few localized sites with moderate disease. The gray line is intended to represent the 8 to 10% of individuals who are on a different path. The X and Y points on Fig. 6 are on two different theoretical periodontitis progression curves, yet to the clinician the periodontal assessment is likely to appear the same. Based on current knowledge of periodontitis, the age differences at time of first clinical diagnosis of mild periodontitis are unlikely to be remarkable. Although current evidence suggests that patients on the gray line are enriched with a small set of clinically important risk factors, and they may be noted by the clinician, there has not been sufficient evidence to manage the cases differently, given the clinical findings of mild periodontitis in both patients at initial examination.

Primary Prevention and Treatment of Mild Periodontitis

Do we have evidence that for patients under the routine care of dentists, individual risk assessment adds value to guide primary periodontitis prevention or treatment of mild periodontitis?

In many ways, this question is really asking the P4 medicine question of whether we can predict which periodontally healthy patients are more likely to be on the gray line than the blue line (**Fig. 6**), because the individual on the gray line is projected to have clinically important progression of periodontitis leading to complications such as tooth loss. Since we already know that most patients, even with only moderate oral hygiene, are likely to develop only mild periodontitis with at the most a few localized sites of moderate disease. So the problem in clinical practice is that a clinician is well justified to approach primary prevention of periodontitis or treatment of mild periodontitis with localized moderate disease with the incorrect assumptions and expectations noted above, because our evidence indicates that most of the patients that dentists see are unlikely to progress to more severe periodontitis and complications whether they are treated more intensively or not. It makes sense for us to alter our current approach to primary periodontitis prevention and treatment of mild disease only if we can do two things: 1) use tools that reliably increase the probability that we can identify an individual patient who is more likely on the gray path rather than the more likely blue path, and 2) we have evidence that a different approach to prevention or early treatment would have made a difference to the individuals on the gray path in terms of complications of more severe periodontitis.

Axelsson and colleagues (2, 99) randomly identified 50-year olds in the Swedish county of Varmland, and performed comprehensive oral examinations at baseline and 10 years later. By report, Axelsson notes that more than 95% of the subjects had regular preventive dental care involving needs-related intervals. As a result of relatively good preventive care during the 10-year period, the mean tooth loss per subject per 10 years was <0.4 teeth, and those patients who lost 2 or more teeth due to clinically confirmed periodontitis were identified. At the 10-year examination buccal swab samples were collected for interleukin-1 genetic analysis. Using two risk factors, smoking and interleukin-1 genotype positive (55), individual patients were stratified by 0, 1, or 2 risk factors, as shown in Fig. 7, and analyzed for frequency of patients losing 2 or more teeth due to periodontitis.

[Figure 7 Here]

Guided by Axelsson's findings, a periodontitis prevention study was designed to ask the following question: In dental patients with no prior diagnosis of periodontitis and none of three previously validated risk factors, do two professional cleanings each year lead to less tooth loss compared to one cleaning annually?(33) And, in patients with pre-defined risk factors do those with two cleanings annually have a lower frequency of tooth loss than those with one cleaning annually?

The clinical validity relative to assignment of individual risk for periodontitis may be assessed by demonstrating that risk stratification of individual patients leads to different outcomes. Important outcomes relative to chronic periodontitis include disease progression, development of complications such as tooth loss, progression following treatment, and impact on selected systemic diseases. As discussed above, risk stratification clinical utility indicates that the risk information can guide specific clinical prevention plans that are more likely to lead to a difference in disease outcomes than managing all patients as if they have the same susceptibility to disease progression. In this study, the predefined specific interventions were one or two clinical examinations and prophylaxes annually in routine dental patients with no history of periodontitis.

[Figure 8 Here]

Since it is not practical to ask the above questions in a randomized controlled clinical trial for more than 10 years in patients undergoing different frequencies of preventive dental care, the investigators adopted the experimental principles recommended for the study and regulatory submission of biomarker performance evidence in previously collected large databases.(97) Study inclusion criteria, endpoints, and risk stratification criteria were predefined (Table 1).

Table 1: Description of Michigan Personalized Prevention Study(33)

1. Potential subjects were selected from a large anonymized dental insurance claims database (Delta Dental of Michigan) guided by predefined criteria. Entrance criteria have been previously reported (33), with some of the key criteria for participation as follows:
    a. Age 35-57 at first dental insurance claim
    b. No history of periodontitis, based on dental claims data
    c. Have employer-based dental insurance through same employer and payor for more than 15 years;
    d. Dental insurance for individuals without periodontitis covered the cost of two examinations and dental prophylaxes annually
    e. Patients attended their dentist of choice consistently for either one or two dental prophylaxes every year for more than 15 years. Criteria for patients with consistent attendance for one prophylaxis annually for 16 consecutive years, or consistent attendance for two annually, are described in the manuscript.(33)
2. 25,452 patients met all criteria for inclusion and were invited to participate, which included consent to access dental insurance claims, consent for specified genetic analysis and submission of a DNA sample, and a medical history. 5,117 patients agreed to participate and all data were complete.
3. All entered patients were classified as either “low risk” or “high risk,” based only on predefined criteria.
    a. Low risk: none of three predefined risk factors: smoking, type 2 diabetes, positive for interleukin-1 genetic variations previously shown to be pro-inflammatory and associated with severe or progressive periodontitis
    b. High Risk: positive for any one of the three predefined risk factors: smoking, type 2 diabetes, interleukin-1 genetic variations
4. Smoking history and diabetes history were collected by patient responses to questionnaires
5. No effort was made to assess the quality of professional cleanings since the study involved several hundred general dentist offices
6. Primary endpoint for analysis was frequency of patients in each risk group with tooth loss during the 16-year monitoring period
7. Primary question: In patients classified as low risk based on having none of the specified three risk factors, did two cleanings annually reduce tooth loss compared to one cleaning annually?

This was a clinical utility study of a predefined risk assessment tool, i.e. presence of any of three risk factors constituted increased risk for tooth loss, and such patients were designated “High Risk.” The study was designed and powered based on the primary clinical utility question. The study was not intended or powered to assess endpoint associations with any single risk factor. The primary clinical utility question was approached as one would for any new technology of potential clinical value. The

primary question therefore involves a simple calculation of frequency of Low Risk patients with tooth loss during the monitoring period of 16 years, depending on whether their preventive regime consisted of one cleaning per year or two cleanings per year.

Table 2: Role of individualized patient risk and frequency of cleanings relative to observed frequency of long-term tooth loss in patients without a history of periodontitis, as reported in the Michigan Personalized Prevention Study (33)

Number of annual prophylaxes	Low Risk n= 2,418	High Risk n= 2,699	High Risk n= 2,699	
			Any 1 risk factor n=2,165	2 or 3 risk factors n=534
1	0.16 [a]	0.22 [b]	0.20 [c]	30 [d]
2	0.14 [a]	0.17 [b]	0.15 [c]	23 [d]

Frequency of patients in the designated risk group who lost 1 or more teeth during the 16 years of dental claims history. [a] In low risk individuals (none of three risk factors), 2 prophylaxes/year was not superior to 1 prophylaxis/year *P*= 0.092; [b] In high risk individuals (one or more of three risk factors), 2 prophylaxes/year was superior to 1 prophylaxis/year *P*= 0.002; [c]In high risk individuals with any one of three risk factors, 2 prophylaxes/year was superior to 1 prophylaxis/year *P*= 0.007; [d]In high risk individuals with any two risk factors or all three risk factors, 2 prophylaxes/year was not superior to 1 prophylaxis/year *P*= 0.108

In this population of adults there appears to be a background level of tooth loss of 14-15% that is not reduced by regular and consistent prophylaxes twice yearly for sixteen years, even in patients with none of the three risk factors. Some of the tooth loss that does not appear to be reduced by regular preventive care may be attributable to conditions, such as root or crown fractures, that do not benefit directly from dental prophylaxes. In addition, in patients with any one of the three prespecified risk factors two cleanings annually reduced tooth loss comparable to the patients who had none of the risk factors. In patients with two or three of the risk factors, two cleanings annually do not appear to be sufficient to reduce tooth loss to the level seen in patients with none or one risk factor.

Can we today identify individual risk for periodontitis? Evidence supports that for adults without a clinical diagnosis of periodontitis, patients can be objectively stratified into two or three risk categories that differentiate clinical responses to different frequencies of preventive care administered in clinical practice by general dentists and hygienists. In this context, a risk profile defined by three risk factors appeared to add value to clinical assessments by the patients' own dentists.

Clinical Scenario 3: Guide treatment and monitoring of periodontitis and secondary prevention

One of the objectives of applying precision medicine to periodontitis, is to be able to identify periodontitis patients who may benefit from more intensive therapy during the primary treatment of periodontitis patients or during the maintenance care of patients. More intensive therapy may include more intensive bacterial control using systemic or local antimicrobials and/or more frequent maintenance care. More intensive therapy may also include enhanced efforts to more effectively control risk factors, such as control of type 2 diabetes, and more direct control of inflammation though drugs(84, 111) or nutritional approaches.(26)

Do we have evidence that individual risk assessment adds value to guide treatment and secondary prevention for patients with periodontitis who are under the routine care of dentists or periodontists?

There are multiple retrospective studies of various risk factors relative to outcomes of periodontal active treatment and maintenance care.(22, 61, 62, 77, 101, 104) These studies were small in size and did not assign a composite risk to each individual patient and then quantify outcomes of treatment based on the individual risk calculated. There was no clear approach to reduce bias. For example, patients with infrequent compliance with maintenance care may reflect overall poor health habits compared to those who attend maintenance visits on a regular frequency. These studies provide good preliminary evidence to guide design of a definitive study of individualized risk for periodontitis and outcomes of treatment. We also do not have the ability from prior studies that looked at periodontitis treatment outcomes to compare the individualized risk to outcomes of different therapies.

Clinical Scenario 4: Guide periodontal treatment to assist prevention and management of certain systemic diseases

Substantial evidence supports an independent influence of periodontitis on certain systemic diseases, including type 2 diabetes, stroke, and coronary artery disease. (8, 9, 19, 48, 121) The periodontitis associations with adverse pregnancy outcomes and rheumatoid arthritis appear to relate directly to specific oral bacterial influences that may be challenging to study relative to the effect of preventing or treating periodontitis.(38, 45, 64, 108)

A very different goal for identifying an individual's risk for periodontitis may be to reduce the likelihood that their periodontitis influences that patient's systemic health. That statement assumes that the systemic influence of periodontitis is not a simple function of the clinical severity of an individual's periodontitis, however the evidence for that conclusion is very limited.

Is there evidence that individual risk assessments add value to guide periodontitis treatment to prevent systemic implications of the periodontitis or improve systemic disease?

The practical question is if we see patients with moderate to severe generalized periodontitis, is there a way to risk stratify the patients to identify which would likely benefit from more intensive treatment and monitoring of the patient to reduce risk for certain systemic diseases and their complications? And is there any evidence that some patients with mild to localized moderate periodontitis can be risk stratified to guide more intensive treatment and monitoring to reduce the risk for certain systemic diseases.

What potential mechanisms most plausibly explain the periodontitis association with other systemic diseases?

When periodontitis is present, two intertwined general mechanisms, inflammation and direct bacterial action, can theoretically activate disease-implicated pathways in various tissues that are distant to the periodontium. One mechanism involves activation of acute phase proteins in the liver that initially help to amplify systemic inflammatory components that broaden protection against the bacterial challenge. The acute phase proteins, such as C-reactive protein, can be activated by bacterial components from

bacteria in the periodontal pocket gaining access through the pocket epithelium to enter the bloodstream and reach and activate hepatocytes. In addition, Inflammatory mediators in gingival tissue may enter circulation and activate the acute phase response. The inflammatory mediators activated in the liver may lead to tissue damage if not switched to a repair mode. Separately, with untreated moderate to severe periodontitis, periodontal bacteria may enter the bloodstream through the pocket wall and potentially localize on damaged tissues, such as denuded vascular endothelium. One could speculate that moderate to severe periodontitis is likely to activate both systemic inflammation directly and also seed periodontal bacteria into the circulation.

Inflammation in an individual's finger, whether activated by a bacterial infection or trauma, can activate the acute phase response in the liver by means of circulating cytokines produced in the initial site of inflammation. Periodontitis activates acute phase protein production and release from the liver, with C-reactive protein being the most well documented. Blood C-reactive protein is higher in individuals with periodontitis (P=0.001), and C-reactive protein level is associated with number of active sites.(21) The more severe and more generalized the periodontitis case, the greater the association with increased C-reactive protein.(74, 96) Patients with severe periodontitis are more likely to have C-reactive protein levels $\geq$ 3mg/L, which is associated with substantial increased risk of cardiovascular diseases.(87) Depending on the severity of the periodontitis and bleeding on probing, sites with more disease have higher scores for periodontal inflamed surface area (85). Based on available evidence, it is reasonable to expect that patients with untreated or inadequately treated moderate to severe periodontitis will be more likely to have elevated C-reactive protein levels and more bacteremias involving periodontal bacteria. In addition, recent evidence indicates that higher periodontal inflamed surface area scores are associated with higher medical costs.(109)

Periodontitis is certainly not the only chronic inflammatory disease associated with increased frequency and severity of other systemic diseases. Several chronic inflammatory diseases that have no direct bacterial component increase blood levels of C-reactive protein and are associated with increased prevalence of certain systemic diseases. Investigators recently used the large UK Clinical Practice Research Datalink to test the role that "systemic inflammatory burden" may play in the initiation of coronary artery disease, stroke, and type 2 diabetes.(20)

[Figure 9 Here]

Several important conclusions can be drawn from the results of this study of chronic inflammation and systemic inflammatory burden. It is clear that certain chronic inflammatory diseases, but not all, increase the risk for type 2 diabetes, coronary artery disease, or strokes. Severity of chronic inflammatory disease appears to be important relative to risk for other diseases; and increased risk for one of the target diseases did not necessarily translate into risk for other target diseases.

Although the evidence is strong for an independent periodontitis influence on certain systemic diseases, we should not assume that we have sufficient understanding of the biologic roles that periodontitis may play to predictably design an intervention study.

It may be that periodontitis of a certain clinical severity has, by itself, a sufficiently strong impact on a systemic disease, such as type 2 diabetes, that intensive treatment of periodontitis will have a predictable effect on type 2 diabetes outcomes. It is also possible that intervention in one complex disease, i.e. periodontitis, may have a range of variations in the target complex disease, i.e. type 2 diabetes, and give variable outcomes.

Fortunately, studies are in progress by multiple groups to explore the complexity of periodontitis at the level of stratifying individual patients by risk for influencing other systemic diseases. For example, severe periodontitis, as defined by clinical measurements was associated with fasting plasma glucose level, as an indication of risk for diabetes. The investigators reported, as shown in Fig. 10, that the significant relationship between severe periodontitis and fasting plasma glucose levels was conditional on the patient also having blood C-reactive protein levels of greater than 3 mg/dL.(12)

[Fig. 10 Here]

Exploration of the potential health benefits of controlling periodontitis requires studies that stratify patients by multiple risk factors to guide intervention and assess outcomes of targeted systemic diseases. Such work is in progress, as has been reported recently and is summarized in Fig. 11.(42)

[Fig. 11 Here]

How can we start to unravel risk profiles that augment the influence of periodontitis on systemic diseases?

One of our primary goals in exploring risk profiles is to help guide the use of periodontitis prevention and treatment to enhance management of certain systemic diseases. Evidence appears to strongly support a role for periodontal bacteria in adverse pregnancy outcomes.(36, 37, 50, 93, 95, 108) That is not to exclude an important role for systemic inflammation, common risk factors, and other elements, but at the moment one can make a good case, based on the evidence that elevated systemic inflammation is a key factor in atherosclerotic cardiovascular disease, strokes, and uncontrolled type 2 diabetes . For practical reasons, this discussion therefore will focus on the potential role of risk factors that influence systemic inflammation as a potential component of the periodontitis influence on certain systemic diseases. The emphasis on systemic inflammation is not to minimize the role of the microbiome in the potential periodontal risk for systemic diseases but merely to allow some focus to the discussion. Others can make a very coherent argument for taking a different approach, and it is likely well justified given our early-stage of development.

The goal is to more precisely target the periodontal patients who more likely benefit from more intensive periodontal disease prevention and management.

There appear to be some dominant concepts as to how risk stratification may be important in assessing an individual periodontal patient's influence on specific systemic diseases.

Concept 1: Periodontitis severity and extent of disease tells the entire story. Other factors may be involved but do not add value beyond periodontitis severity in planning to enhance management of, for example type 2 diabetes, through more intensive treatment of periodontitis.

Concept 2: Common risk factors, such as smoking, that are known to influence both periodontitis and coronary artery disease independently add to or amplify the risk for systemic disease that is attributable to periodontitis alone. This does not discount the importance of periodontitis in the systemic risk but suggests that incorporating the smoking status in a risk profile adds value in planning the treatment of periodontitis for the purpose of helping to control risk for atherosclerotic cardiovascular disease events.

Concept 3: It is a simple systemic inflammatory burden story. Periodontitis is likely an important component of the chronic systemic inflammatory burden that has been implicated in terms of risk for chronic diseases and their complications. The risk profile relative to guiding better management of chronic systemic disease may depend on integrating multiple factors that alter the inflammatory burden and may require control of multiple components in order to reliably influence the systemic disease in question.

Concept 2 and Concept 3 above have some overlap but do lead to different approaches to clinical action. Concept 1, if supported by strong evidence, may allow the periodontist to play an important role in control of chronic diseases, however if Concept 3 is correct the periodontist is likely to become more integrated in health care.

Although periodontitis has a strong independent association with selected systemic diseases, most clearly uncontrolled type 2 diabetes, coronary artery disease, strokes, rheumatoid arthritis, and adverse pregnancy outcomes, the controlled intervention studies that have been undertaken have been generally promising in type 2 diabetes, with some inconsistency that suggests a lack of clear protocol or limited knowledge of relevant disease factors. The intervention studies in adverse pregnancy outcomes have not been rewarding.

Conclusions

individualizing risk of periodontitis is not, in my opinion, simply an interesting academic exercise, but it is perhaps an essential requirement to move the field of periodontitis forward.(56) Thanks to great innovations and efforts by investigators and clinicians throughout the world, we have made great advances in our knowledge but now must move beyond retrospective observations and associations. Stratification of patients in short-term challenge models and in long-term intervention trials are perhaps the only ways to move forward in a process that may differentiate the value of periodontal specialist care. We must identify the complex cases that require different preventive and treatment protocols to demonstrate value in controlling local oral complications of periodontitis and value in assisting the management of chronic systemic diseases.

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Figure Legends

Fig. 1: Clinical research beginning in the 1960's led to a simple concept that rapidly became the dominant approach to preventing and treating gingivitis and periodontitis. The concept of bacterial plaque causation indicated that bacterial accumulations on the teeth, if not removed, initiated gingivitis which transitioned into periodontitis. The concept also suggested that continued bacterial exposure over time would result in severe periodontitis.

Fig. 2: In studies of populations with minimal to no oral hygiene and substantial bacterial accumulations on the teeth, most individuals developed mild periodontitis with localized moderate disease. A smaller group developed severe generalized periodontitis.(6, 70)

Fig. 3: The first and essential step in individualizing risk for periodontitis, and ultimately individualizing prevention and treatment, is having predefined criteria that stratify every patient into well-defined categories that are mutually exclusive.

Fig. 4: Bone regeneration in certain types of periodontal defects was enhanced by the use of recombinant human platelet-derived growth factor BB homodimer (***rhPDGF-BB***), but the substantial long-term regenerative potential was observed primarily in smokers, as noted by amount of bone gain in the platelet-derived growth factor treated smokers (blue solid line) compared to the smokers who received the scaffold alone (green solid line). Linear bone gain figure is reproduced with permission from Nevins et al. *Journal of Periodontology* 2013. (86) The clinical and radiographic images are courtesy of Professor William Giannobile, University of Michigan.

Fig. 5: Periodontal Risk Assessment system as defined by Lang & Tonetti in 2003 (61). The graphical representation of risk uses a spider web image in which each axis of the web is a risk factor and each increment from the center of the web outward allows the clinician to indicate the patient's level of risk for each specific risk factor. The visual image provides a clear impression of a patient's composite risk. The figure is reprinted with permission from Oral Health & Preventive Dentistry. (61)

Fig. 6: Given current knowledge of the epidemiology of periodontitis severity and extent in the U.S., we can postulate 3 curves of periodontitis severity by age. One of those curves (**green**) represents individuals with minimal to no periodontitis through middle age(70) but likely express mild to localized moderate periodontitis in later years.(29) The **blue** line represents individuals who will have mild disease and with appropriate preventive care will develop predominantly mild periodontitis with a few localized sites with moderate disease. The **gray** line is intended to represent the 8 to 10% of individuals who are on a different path.

Fig. 7: Ten-year follow-up in randomly selected 50-year old individuals from one county in Sweden. Most individuals had regular preventive care with their dentist during the 10 years after the initial clinical assessment. The follow-up clinical examinations were used to identify periodontal changes in a well-maintained adult population. In addition, the frequency of patients who lost 2 or more teeth due to clinically confirmed periodontitis were calculated based on two pre-defined risk factors, smoking and

interleukin-1 genotype. [1]Percentage this risk group represented in the total sample (N=276). [2]p=0.0016, Fisher's exact test.(2, 99) Smokers were current smokers at baseline. interleukin-1 genotype positive or negative status was predefined as described previously(33).

Fig. 8: Shows the patient stratifications in the Michigan Personalized Prevention Study. (33) The study outcomes were frequency of patients in each group who lost teeth during the 16 years of claims history.

Fig. 9: Individuals with a prior diagnosis of specific chronic inflammatory diseases were identified in the UK Clinical Practice Research Datalink and were compared by means of a matched cohort study to individuals with no prior diagnosis of any of the listed chronic inflammatory diseases. The study endpoints were frequency of type 2 diabetes, or stroke, or coronary artery disease, in a specific chronic inflammatory disease, such as bullous skin disease, compared to the frequencies in the matched control group of none of the chronic inflammatory diseases.(20) ***P= 0.001; **P< 0.01; *P< 0.05

Fig. 10: Increased severity of periodontitis as represented by quartile of probing depth was associated with increased risk of type 2 diabetes mellitus as assessed by fasting plasma glucose levels greater than or equal to 126mg/dL or prior diagnosis of diabetes. The association was only present in individuals who also had elevated C-reactive protein levels of greater than 3mg/L (12). Data were drawn from NHANES III (n= 5,731; age > 20 years). Figure reproduced with permission from the *Journal of Periodontology*.

Fig. 11: Periodontitis patients who were treated in a specialist clinic but did not respond predictably to standard periodontal therapy and maintenance care had a higher incidence of cardiovascular disease events in long-term follow-up (median 16.8 years). Events included myocardial infarction, stroke, and heart failure. (42)

Abstract

Key breakthroughs in understanding of the etiology and principles of predictable treatment of patients with chronic periodontitis emerged in the late 1960's through the mid-1980's. Unfortunately, some generalizations of the evidence led many to believe that periodontitis was a predictable result of exposure to bacterial plaque accumulations over time. For a brief period, the initial plaque concept was translated by some to implicate specific bacterial infections, with both concepts, plaque exposure and specific infection, being false assumptions that led to clinical outcomes that were frustrating to both the clinician and the patient. The primary misconceptions were that every individual was equally susceptible to periodontitis, that disease severity was a simple function of magnitude of bacterial exposure over time, and that all patients would respond predictably if treated based on the key principles of bacterial reduction and regular maintenance care. We know today that although bacteria are an essential initiating factor, the clinical severity of periodontitis is a complex multifactorial host response to the microbial challenge. The complexity comes from the permutations of different factors that may interact to alter a single individual's host response to challenge, inflammation resolution and repair, and overall outcome to therapy. Fortunately, although there are many permutations that may influence host response and repair, the pathophysiology of chronic periodontitis is generally limited to mild periodontitis with isolated moderate disease in most individuals. However, approximately 20 to 25% of individuals will develop generalized severe periodontitis and likely require more intensive bacterial reduction and different approaches to host modulation of the inflammatory outcomes. This latter group may also have serious systemic implications of their periodontitis. The time appears to be appropriate to

use what we know and currently understand to change our approach to clinical care. Our goal would be to increase our likelihood of identifying the patients who have a more biologically disruptive response combined with a more impactful microbial dysbiosis. Current evidence, albeit limited, indicates that for those individuals we should prevent and treat more intensively. This paper discusses what we know and how we might use that information to start individualizing risk and treat some of our patients in a more targeted manner. In my opinion, we are farther along than many realize, but we have a great lack of prospective clinical evidence that must be accumulated while we continue to unravel the contributions of specific mechanisms.

Figures

Figure 1

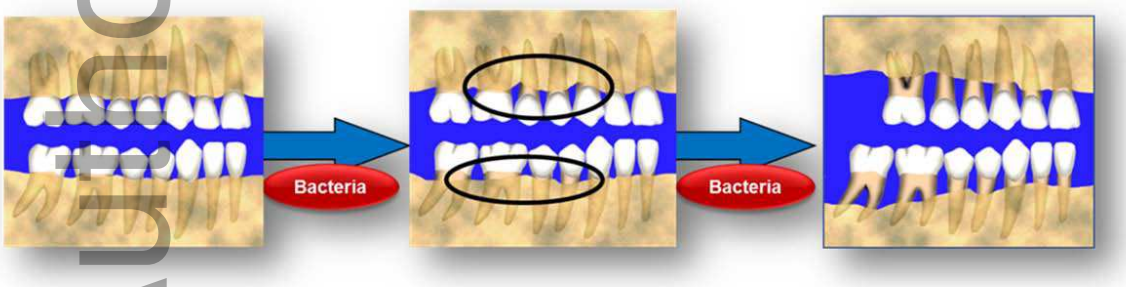


Figure 2

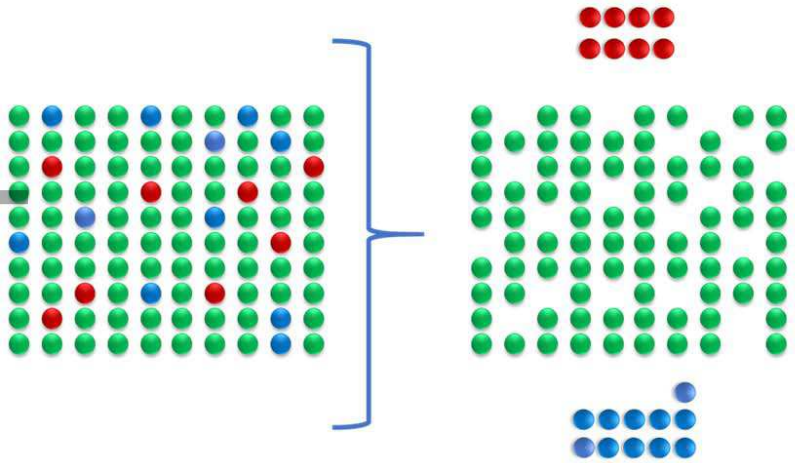


Figure 3

Figure 4

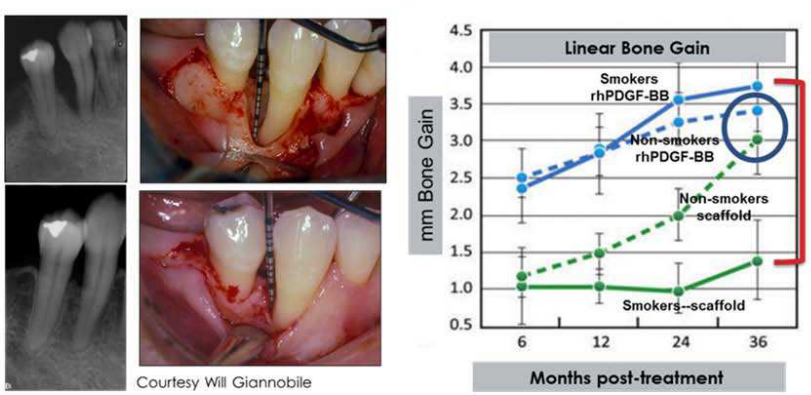


Figure 5

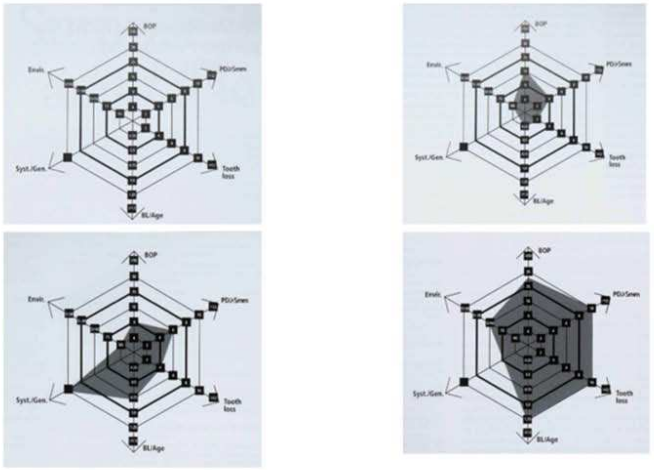


Figure 6

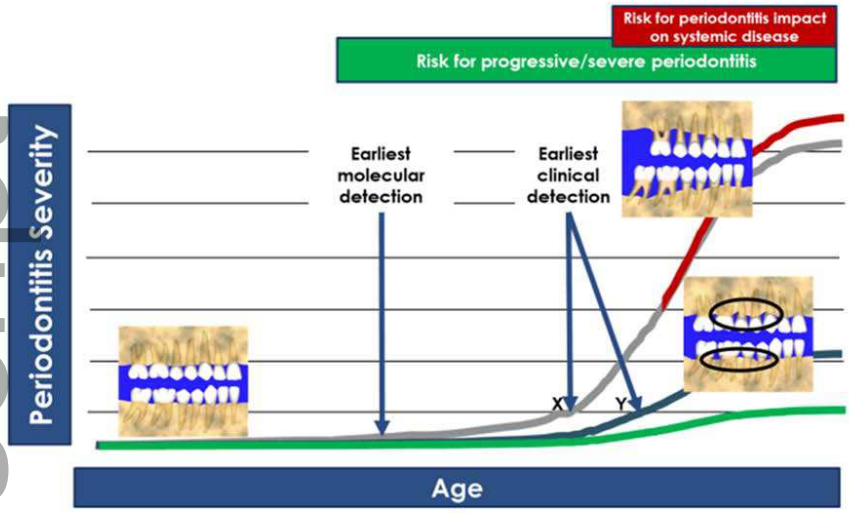


Fig. 7: Tooth loss relative to two risk factors after 10 year prospective follow-up in 50 year-olds

Figure 7

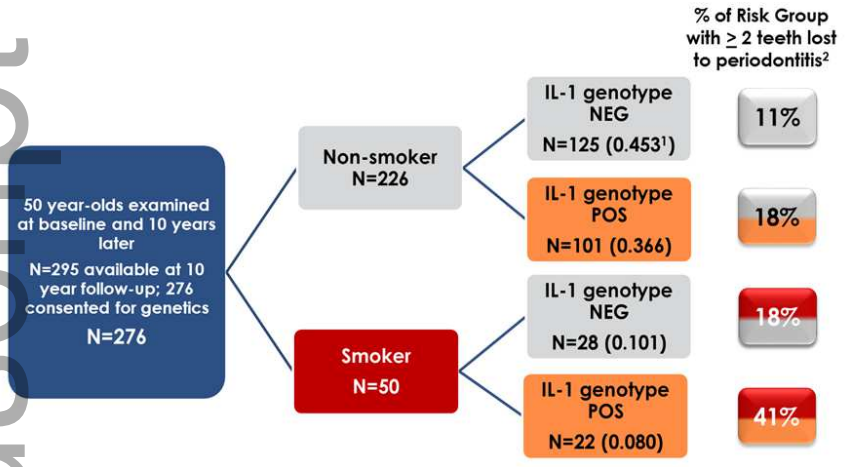


Figure 8

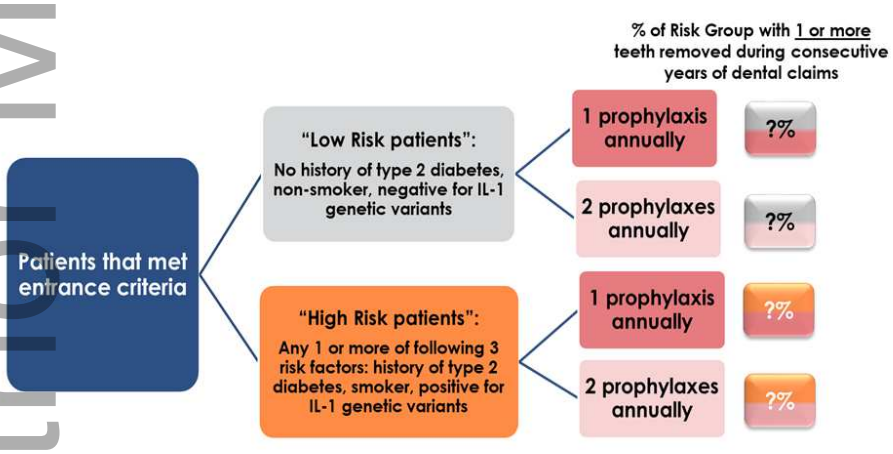
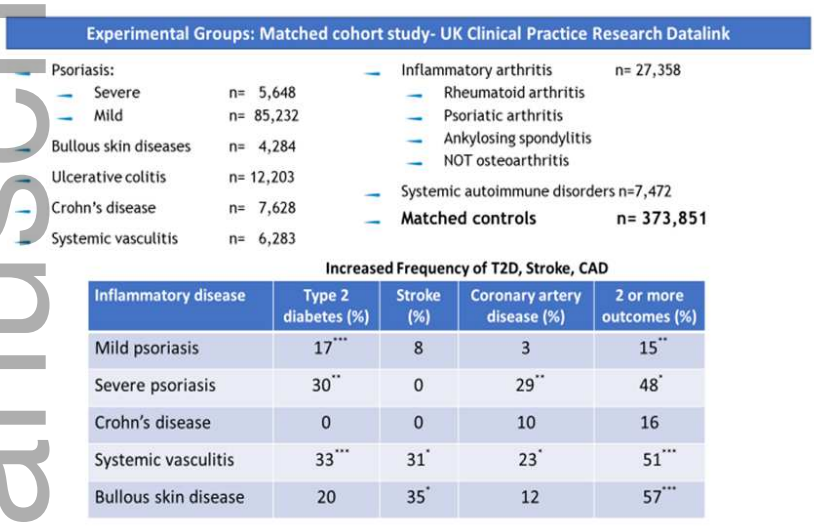


Fig. 9: Individuals with chronic inflammatory diseases have greater frequencies of type 2 diabetes, stroke, and coronary artery disease (20)

Figure 9: Individuals with chronic inflammatory diseases have a greater frequency of type 2 diabetes, stroke, and coronary artery disease (21)

Figure 9



Increased Frequency of T2D, Stroke, CAD

Inflammatory disease	Type 2 diabetes (%)	Stroke (%)	Coronary artery disease (%)	2 or more outcomes (%)
Mild psoriasis	17***	8	3	15**
Severe psoriasis	30**	0	29**	48*
Crohn's disease	0	0	10	16
Systemic vasculitis	33***	31*	23*	51***
Bullous skin disease	20	35*	12	57***

Fig. 10: Individuals with severe periodontitis had increased risk for type 2 diabetes mellitus but it was conditional on elevated C-reactive protein

Figure 10

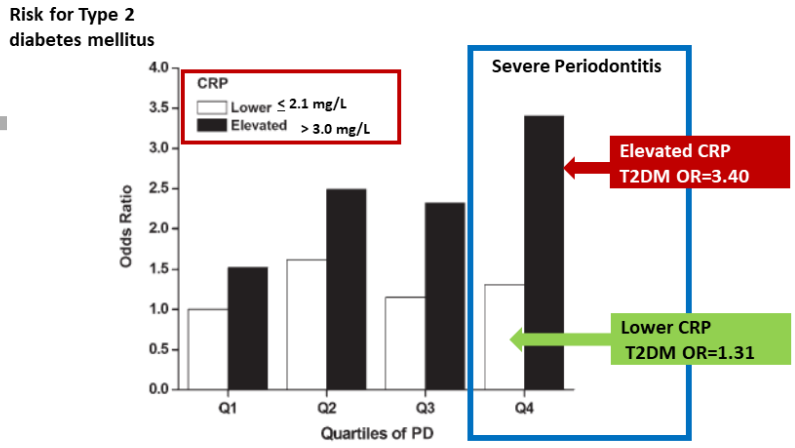


Fig. 11: A poor response to periodontitis treatment may predict future cardiovascular disease

Figure 11

- 5,297 periodontitis patients treated in periodontal clinic
- Treatment:
  - Oral hygiene instruction
  - Non-surgical treatment phase
  - Re-evaluation
  - Residual pockets rescaled or surgically treated
  - Maintenance program
- 1 yr evaluation after active treatment: "Poor responder" if
  - >10% residual pockets >4mm, AND
  - ≥20% sites with bleeding on probing