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(54) Title: MULTI-ANALYTE ANALYSIS OF SALIVA BIOMARKERS AS PREDICTORS OF PERIODONTAL AND PERI-IMPLANT DISEASE

(57) Abstract: The present invention relates to methods of measuring biomarkers to determine the probability of a periodontal and/or peri-implant disease. More specifically, the invention provides a panel of biomarkers that, when used in combination, can allow determination of the probability of a periodontal and/or peri-implant disease state with extremely high accuracy.

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MULTI-ANALYTE ANALYSIS OF SALIVA BIOMARKERS AS PREDICTORS OF PERIODONTAL AND PERI-IMPLANT DISEASE

STATEMENT OF GOVERNMENT INTEREST

[0001] This invention was made with Government support under grant number U01-DE014961 awarded by The National Institute of Dental and Craniofacial Research (NIDCR), and grant number M01-RR000042, awarded by The National Center for Research Resources (NCRR). The Government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] This application claims priority of U.S. Provisional Application No. 60/962,656 filed July 30, 2007 and is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present invention relates to methods of measuring biomarkers to determine the probability of a periodontal and/or peri-implant disease. More specifically, the invention provides a panel of biomarkers that, when used in combination, can allow determination of the probability of a periodontal and/or peri-implant disease state with extremely high accuracy.

BACKGROUND OF THE INVENTION

[0004] Periodontal diseases are the leading cause of tooth loss in adults. Periodontitis is initiated by tooth-associated subgingival biofilms trigger an altered host response leading to soft tissue inflammation and subsequent bone loss. Periodontal infections are implicated in a variety of other diseases (such as cardiovascular disease, stroke and aspiration pneumonia) whereby the microbial biofilm serves as a "slow delivery system" of oral pathogens adhering to teeth leading to a chronic microbial challenge and downstream effects of an altered host response to the patient. Diagnostic methods in clinical practice today lack the ability to both detect the onset of inflammation and to identify those patients susceptible to future disease progression. Oral-fluid-based point-of-care (POC) diagnostics are commonly used for various diagnostic tests in medicine and more recently are being adapted for the determination of oral diseases (Tabak, 2007, *Ann N Y Acad Sci* 1098: 7-14). Recent clinical applications use new "lab-on-a-chip, LOC" technologies as rapid POC diagnostics of systemic infectious diseases (Chen *et al.*, 2007, *Ann N Y Acad Sci* 1098: 429-436; Mauk *et al.*, 2007, *Ann N Y Acad Sci* 1098: 467-475) and periodontal disease (Herr *et al.*, 2007, *Proc Natl Acad Sci U S A* 104: 5268-5273). The human salivary proteome project, supported by the U.S. National Institute of Craniofacial Research (NIDCR), has further generated emphasis

on the use of proteomic markers for disease diagnosis (Wong, 2006, J Am Dent Assoc 137: 313-321).

[0005] In oral-based diagnostics, the use of oral fluids has successfully demonstrated its ease of use for POC application (Malamud, 2006, J Am Dent Assoc 137: 284-286) for the detection of oral cancer (Li *et al.*, 2004, Clin Cancer Res 10: 8442-8450; Zimmermann *et al.*, 2008, Oral Oncol. 44(5):425-9) or HIV infection (Delaney *et al.*, 2006, Aids 20: 1655-1660). Furthermore, the use of microfluidic devices as examples of LOC technology offers significant potential for rapid saliva diagnosis for widespread public health purposes (Herr *et al.*, 2007, Proc Natl Acad Sci U S A 104: 5268-5273; Yager *et al.*, 2006, Nature 442: 412-418). However, for periodontal disease determination, most research to date has focused primarily on gingival crevicular fluid (GCF) biomarkers that provide local disease status, but represent a cumbersome, difficult to utilize approach for clinical application (Taba *et al.*, 2005, Dent Clin North Am 49: 551-571, vi). Easy-to-access saliva contains both locally and systemically-derived mediators of periodontal disease and thus offers significant potential for the assessment of periodontal disease status and risk (Kinney *et al.*, 2007, Ann N Y Acad Sci 1098: 230-251).

[0006] Periodontal and peri-implant disease activity presently are diagnosed by clinical parameters such as pocket depth, bleeding on probing, and radiographs. These parameters have limitations in that they lack ability to predict future attachment loss, and provide information only on the existence of past disease activity. The need for diagnostics in clinical dentistry that are predictive markers of active periodontitis is a focus of present research. Periodontal disease is a general term used to describe specific diseases that affect the gingiva, as well as the supporting connective tissues and alveolar bone that anchor the teeth in the jaws. The periodontal diseases are among the most common infectious diseases in humans. In the last fifteen years, with the decline of dental caries in children aged 6-18, and better prevention programs for the general population, periodontal disease leading to tooth loss has assumed even greater importance.

[0007] As more teeth are retained due to reduced cavities, more teeth are at risk to be affected by periodontal disease.

[0008] The use of clinical parameters for the diagnosis of periodontal disease has numerous limitations. For example, Haffajee and co-workers ("Clinical risk indicators for periodontal attachment loss," Journal of Clinical Periodontology, 1991; v.18:117-125) have demonstrated that no clinical parameters have been shown to be predictive for periodontal

disease activity. Thus, there have been intensive research efforts to develop diagnostic tests for periodontal disease evaluation. Over 60 different tests for oral fluid components have been studied with no single oral fluid biomarker demonstrating utility as a clinically available diagnostic (reviewed in Taba et al, "Diagnostic biomarkers for oral and periodontal diseases," Dental Clinics of North America, 2005; v.49:551-571).

[0009] Despite the plethora of such components, there are at present no diagnostic tests available which have been demonstrated to be highly predictive for periodontal disease. As the breakdown of these components is the ultimate concern of the practitioner, their destruction should be evaluated.

[0010] Thus, the recognition and diagnosis of periodontal disease has become even more important, and there exists a need in the art for rapid, accurate and sensitive methods for diagnosing and assessing the degree of periodontal diseases.

SUMMARY OF THE INVENTION

[0011] The present invention demonstrates a role for biomarker levels as an indicator of oral disease. Work described herein demonstrates that elevated levels of multiple biomarkers can be used as a tool for accurately and rapidly determining the probability of oral disease.

[0012] Thus, the present invention provides methods for determining the probability of an oral disease state comprising the step of determining the levels of two or more biomarkers in a sample from a first individual, said levels of said two or more biomarkers indicating the probability of said oral disease state.

[0013] The present invention also provides diagnostic methods wherein the levels of two or more biomarkers are indicative of oral disease if said levels of said two or more biomarkers from said first individual are elevated compared to levels of identical biomarkers from a second individual.

[0014] The present invention also provides methods for determining susceptibility to oral disease wherein the levels of two or more biomarkers are indicative of susceptibility to oral disease if said levels of said two or more biomarkers from a first individual are elevated compared to levels of identical biomarkers from a second individual.

[0015] The present invention further provides methods wherein the levels of two or more biomarkers are indicative of susceptibility to oral disease if said levels of said two or more biomarkers from a first individual are elevated compared to biomarker levels in a sample from the first individual measured at an earlier time point.

[0016] The present invention also provides methods wherein the levels of two or more biomarkers are indicative of progression of oral disease if said levels of said two or more biomarkers from a first individual are elevated compared to biomarker levels in a sample from the first individual measured at an earlier time point.

[0017] The present invention additionally provides methods for determining effectiveness of oral disease treatment wherein the levels of said two or more biomarkers are indicative of effective oral disease treatment if said levels of said two or more biomarkers from a first individual are decreased compared to levels of identical biomarkers from the same individual measured at an earlier time point.

[0018] In one aspect, the invention provides methods wherein the occurrence of an oral disease is diagnosed at a probability equal to or greater than 70%.

[0019] In another aspect, methods are provided wherein the occurrence of an oral disease is diagnosed at a probability equal to or greater than 80%.

[0020] In still another aspect, methods are provided wherein the occurrence of an oral disease is diagnosed at a probability equal to or greater than 90%.

[0021] In an aspect of the methods, the levels of two biomarkers are determined and used to calculate the probability of oral disease.

[0022] In other aspects of the methods, the levels of three, four, or five biomarkers are determined and used to calculate the probability of oral disease.

[0023] In still other aspects of the methods, the levels of six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, twenty or more biomarkers are determined and used to calculate the probability of oral disease.

[0024] In various aspects of methods of the invention, the two or more biomarkers are selected from the group consisting of *Aggregatibacter actinomycetemcomitans*, *Campylobacter rectus*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, matrix metalloproteinase-8 (MMP-8), matrix metalloproteinase-9 (MMP-9), osteoprotegerin (OPG), type I collagen pyridinoline cross-linked telopeptide (ICTP), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), interleukin-4 (IL-4), interleukin-10 (IL-10), interleukin-2 (IL-2), interleukin-13 (IL-13), calprotectin, tumor necrosis factor α (TNF α) and combinations thereof.

[0025] In various embodiments of the methods, the two or more biomarkers include the combinations of biomarkers : Calprotectin + MMP9, MMP8 + Calprotectin, MMP8 + ICTP,

MMP9 + TNFa, MMP9 + ICTP, MMP8 + TNFa, MMP8 + OPG, MMP9 + OPG, MMP8 + IL1beta, MMP8 + MMP9, MMP8 + IL10, MMP9 + IL1beta, MMP9 + IL6, MMP8 + IL4, MMP9 + IL4, MMP8 + IL6, MMP8 + IL2, MMP9 + IL10, MMP9 + IL2, MMP9 + IL13, MMP8 + IL13, Calprotectin + IL6, Calprotectin + OPG, Calprotectin + ICTP, Calprotectin + IL4, Calprotectin + IL10, IL6 + ICTP, Calprotectin + IL1beta, Calprotectin + IL2, Calprotectin + TNFa, Calprotectin + IL13, IL6 + TNFa, OPG + IL6, IL6 + IL4, IL6 + IL13, ICTP + IL4, ICTP + IL1beta, ICTP + IL10, IL6 + IL1beta, IL6 + IL2, IL4 + TNFa, OPG + ICTP, IL6 + IL10, ICTP + TNFa, ICTP + IL2, OPG + IL4, IL13 + IL4, ICTP + IL13, IL10 + IL4, IL1beta + IL4, IL2 + IL4, OPG + IL1beta, OPG + IL10, IL1beta + TNFa, IL10 + IL13, IL1beta + IL10, IL10 + TNFa, IL10 + IL2, IL1beta + IL2, OPG + IL2, OPG + TNFa, IL1beta + IL13, IL2 + TNFa, OPG + IL13, IL2 + IL13, IL13 + TNFa, Calprotectin + MMP9 + OPG, Calprotectin + MMP9 + ICTP, Calprotectin + MMP9 + TNFa, MMP8 + Calprotectin + OPG, Calprotectin + MMP9 + IL1beta, Calprotectin + MMP9 + IL10, Calprotectin + MMP9 + IL6, MMP8 + ICTP + TNFa, MMP8 + Calprotectin + MMP9, MMP8 + Calprotectin + ICTP, Calprotectin + MMP9 + IL4, MMP8 + Calprotectin + IL10, Calprotectin + MMP9 + IL2, Calprotectin + MMP9 + IL13, MMP8 + Calprotectin + TNFa, MMP8 + MMP9 + TNFa, MMP8 + Calprotectin + IL6, MMP8 + OPG + ICTP, MMP9 + ICTP + TNFa, MMP8 + ICTP + IL10, MMP8 + Calprotectin + IL1beta, MMP8 + IL6 + ICTP, MMP8 + ICTP + IL1beta, MMP8 + Calprotectin + IL4, MMP8 + Calprotectin + IL2, MMP8 + MMP9 + ICTP, MMP8 + ICTP + IL4, MMP9 + OPG + TNFa, MMP9 + IL4 + TNFa, MMP8 + ICTP + IL2, MMP9 + IL6 + TNFa, MMP8 + ICTP + IL13, MMP8 + Calprotectin + IL13, MMP8 + IL2 + TNFa, MMP8 + MMP9 + IL1beta, MMP9 + IL6 + ICTP, MMP9 + IL10 + TNFa, MMP8 + OPG + TNFa, MMP8 + IL10 + TNFa, MMP9 + OPG + ICTP, MMP9 + IL2 + TNFa, MMP9 + ICTP + IL1beta, MMP8 + OPG + IL10, MMP8 + IL4 + TNFa, MMP9 + ICTP + IL10, MMP9 + IL13 + TNFa, MMP8 + MMP9 + OPG, MMP8 + IL1beta + IL10, MMP9 + ICTP + IL4, MMP9 + ICTP + IL2, MMP8 + IL6 + TNFa, MMP9 + IL1beta + TNFa, MMP8 + OPG + IL6, MMP9 + ICTP + IL13, MMP8 + IL1beta + IL4, MMP8 + OPG + IL4, MMP8 + IL1beta + TNFa, MMP8 + OPG + IL1beta, MMP8 + IL13 + TNFa, MMP8 + OPG + IL13, MMP8 + MMP9 + IL6, MMP9 + OPG + IL1beta, MMP8 + MMP9 + IL13, MMP8 + OPG + IL2, MMP8 + IL1beta + IL2, MMP9 + IL6 + IL1beta, MMP9 + OPG + IL2, MMP9 + OPG + IL6, MMP9 + OPG + IL4, MMP8 + IL1beta + IL13, MMP9 + OPG + IL10, MMP8 + IL10 + IL13, MMP9 + IL1beta + IL10, MMP9 + IL1beta + IL4, MMP8 + IL6 + IL1beta, MMP8 + MMP9 + IL10, MMP9 + IL1beta + IL13, MMP9 + OPG + IL13, MMP9 + IL6 + IL4, MMP8 + IL10 + IL2, MMP8 + IL10 + IL4, MMP8 + IL6 + IL10, MMP8 + MMP9 + IL4, MMP9 + IL6 + IL2, MMP9 + IL6 + IL13, MMP8 + MMP9 + IL2, MMP8 + IL6 + IL4, MMP9 +

IL1beta + IL2, MMP9 + IL2 + IL4, MMP8 + IL13 + IL4, MMP9 + IL13 + IL4, MMP9 + IL6 + IL10, MMP8 + IL2 + IL4, MMP8 + IL2 + IL13, MMP9 + IL10 + IL13, MMP9 + IL10 + IL4, MMP8 + IL6 + IL2, MMP9 + IL10 + IL2, MMP8 + IL6 + IL13, Calprotectin + IL6 + TNFa, MMP9 + IL2 + IL13, Calprotectin + OPG + ICTP, Calprotectin + IL6 + ICTP, Calprotectin + OPG + IL6, Calprotectin + IL6 + IL13, IL6 + ICTP + IL13, Calprotectin + ICTP + IL4, Calprotectin + OPG + IL4, Calprotectin + OPG + IL1beta, Calprotectin + ICTP + IL10, Calprotectin + IL6 + IL1beta, Calprotectin + IL6 + IL2, Calprotectin + IL6 + IL10, IL6 + ICTP + TNFa, Calprotectin + IL6 + IL4, OPG + IL6 + ICTP, Calprotectin + ICTP + TNFa, IL6 + IL4 + TNFa, Calprotectin + OPG + IL10, Calprotectin + ICTP + IL1beta, Calprotectin + ICTP + IL2, Calprotectin + IL4 + TNFa, Calprotectin + OPG + IL2, Calprotectin + IL13 + IL4, Calprotectin + ICTP + IL13, Calprotectin + OPG + TNFa, Calprotectin + IL10 + IL2, Calprotectin + OPG + IL13, Calprotectin + IL10 + IL4, Calprotectin + IL1beta + IL4, Calprotectin + IL1beta + IL10, Calprotectin + IL10 + IL13, Calprotectin + IL1beta + TNFa, Calprotectin + IL2 + IL4, IL6 + ICTP + IL4, Calprotectin + IL10 + TNFa, IL6 + IL13 + IL4, ICTP + IL4 + TNFa, Calprotectin + IL1beta + IL13, IL6 + ICTP + IL1beta, Calprotectin + IL1beta + IL2, IL6 + ICTP + IL10, Calprotectin + IL2 + TNFa, IL6 + ICTP + IL2, Calprotectin + IL2 + IL13, ICTP + IL13 + IL4, IL6 + IL10 + TNFa, OPG + IL6 + IL13, Calprotectin + IL13 + TNFa, IL6 + IL1beta + TNFa, IL6 + IL2 + IL13, OPG + IL4 + TNFa, OPG + IL6 + IL4, OPG + IL6 + TNFa, OPG + IL6 + IL1beta, IL6 + IL1beta + IL13, IL10 + IL13 + IL4, IL2 + IL4 + TNFa, ICTP + IL2 + TNFa, IL10 + IL4 + TNFa, ICTP + IL2 + IL4, OPG + ICTP + IL4, ICTP + IL10 + IL13, IL6 + IL10 + IL4, IL6 + IL2 + TNFa, ICTP + IL1beta + IL4, OPG + IL6 + IL2, IL6 + IL1beta + IL4, IL6 + IL2 + IL4, OPG + IL6 + IL10, ICTP + IL1beta + TNFa, ICTP + IL10 + IL4, ICTP + IL10 + TNFa, OPG + ICTP + IL1beta, IL6 + IL13 + TNFa, IL6 + IL10 + IL13, ICTP + IL1beta + IL10, IL1beta + IL2 + TNFa, OPG + ICTP + IL10, IL1beta + IL4 + TNFa, ICTP + IL10 + IL2, ICTP + IL1beta + IL2, ICTP + IL1beta + IL13, IL13 + IL4 + TNFa, IL6 + IL10 + IL2, OPG + ICTP + IL2, OPG + ICTP + TNFa, IL1beta + IL13 + IL4, OPG + ICTP + IL13, IL6 + IL1beta + IL2, OPG + IL13 + IL4, IL6 + IL1beta + IL10, IL10 + IL2 + IL13, ICTP + IL13 + TNFa, OPG + IL10 + IL4, ICTP + IL2 + IL13, OPG + IL1beta + IL4, OPG + IL2 + IL4, IL2 + IL13 + IL4, OPG + IL10 + TNFa, OPG + IL1beta + IL13, OPG + IL10 + IL13, OPG + IL1beta + IL2, OPG + IL1beta + TNFa, OPG + IL10 + IL2, IL10 + IL2 + IL4, IL1beta + IL10 + IL4, IL1beta + IL10 + IL13, IL1beta + IL10 + TNFa, OPG + IL2 + TNFa, IL1beta + IL2 + IL4, OPG + IL1beta + IL10, IL10 + IL2 + TNFa, IL1beta + IL10 + IL2, IL10 + IL13 + TNFa, IL1beta + IL13 + TNFa, OPG + IL13 + TNFa, IL1beta + IL2 + IL13, OPG + IL2 + IL13, IL2 + IL13 + TNFa, T.denticola + P.intermedia, T.denticola + C.rectus, T.forsythia + T.denticola,

P.gingivalis + P.intermedia, T.forsythia + P.intermedia, P.gingivalis + T.denticola,
 T.denticola + F.nucleatum, P.gingivalis + T.forsythia, T.forsythia + F.nucleatum, T.forsythia
 + C.rectus, P.gingivalis + F.nucleatum, P.gingivalis + C.rectus, P.intermedia + F.nucleatum,
 P.intermedia + C.rectus, F.nucleatum + C.rectus, T.forsythia + T.denticola + P.intermedia,
 P.gingivalis + T.denticola + P.intermedia, T.denticola + P.intermedia + C.rectus, T.denticola
 + P.intermedia + F.nucleatum, T.forsythia + T.denticola + C.rectus, P.gingivalis + T.forsythia
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 + C.rectus, IL2 + C.rectus, IL13 + C.rectus, IL4 + F.nucleatum, TNFa + C.rectus, IL10 +
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 F.nucleatum, IL13 + F.nucleatum, T.denticola + ICTP + C.rectus, T.denticola + ICTP +
 P.intermedia, MMP8 + T.denticola + P.intermedia, T.forsythia + T.denticola + ICTP, MMP9
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 P.gingivalis + T.denticola + ICTP, Calprotectin + T.denticola + C.rectus, T.denticola + IL13
 + P.intermedia, MMP8 + T.forsythia + T.denticola, MMP8 + T.forsythia + P.intermedia,

MMP9 + T.forsythia + T.denticola, T.denticola + ICTP + F.nucleatum, MMP8 + P.gingivalis + T.denticola, MMP9 + P.gingivalis + T.denticola, Calprotectin + P.gingivalis + P.intermedia, MMP9 + P.gingivalis + P.intermedia, OPG + T.denticola + P.intermedia, T.denticola + TNFa + P.intermedia, T.denticola + IL4 + P.intermedia, Calprotectin + T.forsythia + P.intermedia, MMP9 + T.forsythia + P.intermedia, T.denticola + IL6 + P.intermedia, T.denticola + IL6 + C.rectus, T.denticola + IL1beta + P.intermedia, MMP8 + T.denticola + F.nucleatum, MMP9 + T.denticola + F.nucleatum, T.denticola + IL2 + P.intermedia, T.denticola + IL10 + C.rectus, T.denticola + IL10 + P.intermedia, T.forsythia + IL13 + P.intermedia, OPG + T.denticola + C.rectus, OPG + T.forsythia + T.denticola, T.forsythia + T.denticola + IL13, Calprotectin + T.forsythia + T.denticola, P.gingivalis + ICTP + P.intermedia, T.denticola + IL2 + C.rectus, MMP8 + P.gingivalis + T.forsythia, MMP9 + P.gingivalis + T.forsythia, T.forsythia + ICTP + P.intermedia, T.denticola + IL13 + C.rectus, MMP9 + T.forsythia + C.rectus, T.forsythia + TNFa + P.intermedia, T.denticola + IL4 + C.rectus, T.denticola + TNFa + C.rectus, T.forsythia + T.denticola + TNFa, T.denticola + IL1beta + C.rectus, T.forsythia + T.denticola + IL1beta, OPG + P.gingivalis + T.denticola, MMP8 + T.forsythia + C.rectus, T.forsythia + T.denticola + IL6, P.gingivalis + IL13 + P.intermedia, T.forsythia + T.denticola + IL4, T.forsythia + IL10 + P.intermedia, MMP9 + T.forsythia + F.nucleatum, Calprotectin + T.forsythia + C.rectus, P.gingivalis + IL6 + P.intermedia, MMP8 + T.forsythia + F.nucleatum, T.forsythia + IL1beta + P.intermedia, T.forsythia + T.denticola + IL10, T.forsythia + T.denticola + IL2, OPG + T.forsythia + P.intermedia, MMP9 + P.gingivalis + C.rectus, T.forsythia + IL4 + P.intermedia, MMP9 + P.gingivalis + F.nucleatum, OPG + P.gingivalis + P.intermedia, T.forsythia + IL6 + P.intermedia, Calprotectin + T.denticola + F.nucleatum, P.gingivalis + T.denticola + IL13, P.gingivalis + IL1beta + P.intermedia, P.gingivalis + TNFa + P.intermedia, Calprotectin + P.gingivalis + T.denticola, MMP8 + P.gingivalis + F.nucleatum, P.gingivalis + IL2 + P.intermedia, MMP8 + P.gingivalis + C.rectus, Calprotectin + T.forsythia + F.nucleatum, P.gingivalis + IL4 + P.intermedia, T.forsythia + IL2 + P.intermedia, P.gingivalis + T.forsythia + IL6, P.gingivalis + T.denticola + IL6, P.gingivalis + IL10 + P.intermedia, P.gingivalis + T.denticola + IL10, P.gingivalis + T.denticola + IL2, Calprotectin + P.gingivalis + T.forsythia, OPG + T.denticola + F.nucleatum, P.gingivalis + T.forsythia + ICTP, T.forsythia + ICTP + F.nucleatum, P.gingivalis + T.denticola + IL4, T.denticola + IL6 + F.nucleatum, T.forsythia + ICTP + C.rectus, T.denticola + IL2 + F.nucleatum, Calprotectin + P.gingivalis + C.rectus, P.gingivalis + T.denticola + TNFa, OPG + P.gingivalis + T.forsythia, P.gingivalis + T.forsythia + IL13, T.denticola + IL13 + F.nucleatum, T.denticola + IL10 + F.nucleatum, Calprotectin + P.gingivalis + F.nucleatum, P.gingivalis + T.forsythia

+ IL10, P.gingivalis + T.denticola + IL1beta, T.forsythia + IL6 + C.rectus, T.forsythia + IL13 + F.nucleatum, T.forsythia + IL13 + C.rectus, T.forsythia + IL6 + F.nucleatum, T.denticola + IL4 + F.nucleatum, OPG + T.forsythia + F.nucleatum, T.forsythia + TNFa + F.nucleatum, P.gingivalis + IL6 + F.nucleatum, T.denticola + IL1beta + F.nucleatum, OPG + T.forsythia + C.rectus, T.denticola + TNFa + F.nucleatum, T.forsythia + IL1beta + F.nucleatum, P.gingivalis + T.forsythia + IL2, T.forsythia + IL1beta + C.rectus, P.gingivalis + ICTP + F.nucleatum, T.forsythia + IL4 + F.nucleatum, T.forsythia + TNFa + C.rectus, P.gingivalis + T.forsythia + IL4, P.gingivalis + IL6 + C.rectus, T.forsythia + IL4 + C.rectus, T.forsythia + IL2 + F.nucleatum, P.gingivalis + T.forsythia + TNFa, T.forsythia + IL10 + F.nucleatum, T.forsythia + IL10 + C.rectus, P.gingivalis + ICTP + C.rectus, T.forsythia + IL2 + C.rectus, P.gingivalis + T.forsythia + IL1beta, P.gingivalis + IL10 + F.nucleatum, OPG + P.gingivalis + F.nucleatum, P.gingivalis + IL4 + F.nucleatum, P.gingivalis + IL2 + F.nucleatum, P.gingivalis + IL1beta + F.nucleatum, P.gingivalis + TNFa + F.nucleatum, P.gingivalis + IL13 + F.nucleatum, OPG + P.gingivalis + C.rectus, MMP8 + P.intermedia + F.nucleatum, P.gingivalis + IL10 + C.rectus, P.gingivalis + IL2 + C.rectus, MMP8 + P.intermedia + C.rectus, P.gingivalis + IL4 + C.rectus, P.gingivalis + TNFa + C.rectus, P.gingivalis + IL1beta + C.rectus, P.gingivalis + IL13 + C.rectus, Calprotectin + P.intermedia + F.nucleatum, MMP9 + P.intermedia + F.nucleatum, MMP9 + P.intermedia + C.rectus, Calprotectin + P.intermedia + C.rectus, ICTP + P.intermedia + F.nucleatum, TNFa + P.intermedia + F.nucleatum, IL4 + P.intermedia + F.nucleatum, ICTP + P.intermedia + C.rectus, IL10 + P.intermedia + F.nucleatum, IL1beta + P.intermedia + F.nucleatum, IL6 + P.intermedia + F.nucleatum, OPG + P.intermedia + F.nucleatum, IL2 + P.intermedia + F.nucleatum, IL13 + P.intermedia + F.nucleatum, MMP9 + F.nucleatum + C.rectus, TNFa + P.intermedia + C.rectus, MMP8 + F.nucleatum + C.rectus, IL4 + P.intermedia + C.rectus, Calprotectin + F.nucleatum + C.rectus, IL6 + P.intermedia + C.rectus, IL10 + P.intermedia + C.rectus, IL1beta + P.intermedia + C.rectus, IL13 + P.intermedia + C.rectus, IL2 + P.intermedia + C.rectus, OPG + P.intermedia + C.rectus, ICTP + F.nucleatum + C.rectus, IL6 + F.nucleatum + C.rectus, IL4 + F.nucleatum + C.rectus, IL10 + F.nucleatum + C.rectus, IL13 + F.nucleatum + C.rectus, IL1beta + F.nucleatum + C.rectus, TNFa + F.nucleatum + C.rectus, OPG + F.nucleatum + C.rectus, IL2 + F.nucleatum + C.rectus, MMP8 + T.denticola + ICTP, MMP9 + T.denticola + ICTP, T.denticola + IL6 + ICTP, Calprotectin + T.denticola + ICTP, T.denticola + ICTP + IL10, MMP8 + OPG + T.denticola, MMP8 + T.denticola + IL1beta, OPG + T.denticola + ICTP, Calprotectin + MMP9 + P.gingivalis, MMP9 + OPG + T.denticola, Calprotectin + MMP9 + T.denticola, MMP9 + T.denticola + IL1beta, T.denticola + ICTP + IL13, T.denticola + ICTP + IL2, MMP8 + Calprotectin + T.denticola, T.denticola +

ICTP + TNFa, MMP8 + T.denticola + IL2, MMP9 + T.denticola + TNFa, MMP8 + Calprotectin + P.gingivalis, MMP8 + T.denticola + IL10, MMP8 + T.denticola + TNFa, MMP8 + T.denticola + IL13, Calprotectin + MMP9 + T.forsythia, MMP9 + T.denticola + IL13, T.denticola + ICTP + IL4, MMP8 + P.gingivalis + ICTP, MMP9 + T.denticola + IL6, MMP9 + T.denticola + IL2, T.denticola + ICTP + IL1beta, MMP8 + MMP9 + T.denticola, MMP9 + T.denticola + IL10, MMP8 + T.denticola + IL6, MMP8 + T.denticola + IL4, MMP9 + T.denticola + IL4, MMP8 + T.forsythia + ICTP, MMP9 + P.gingivalis + ICTP, MMP8 + T.forsythia + IL1beta, MMP9 + T.forsythia + ICTP, MMP8 + Calprotectin + T.forsythia, MMP8 + OPG + T.forsythia, MMP9 + OPG + T.forsythia, MMP9 + T.forsythia + IL1beta, MMP9 + T.forsythia + TNFa, MMP9 + T.forsythia + IL13, MMP8 + T.forsythia + IL13, MMP8 + T.forsythia + TNFa, MMP9 + OPG + P.gingivalis, MMP9 + P.gingivalis + IL1beta, MMP9 + P.gingivalis + IL6, MMP8 + OPG + P.gingivalis, MMP8 + P.gingivalis + IL6, MMP8 + P.gingivalis + IL10, MMP8 + P.gingivalis + IL1beta, MMP8 + T.forsythia + IL4, MMP9 + T.forsythia + IL4, Calprotectin + OPG + T.denticola, MMP9 + P.gingivalis + TNFa, MMP8 + P.gingivalis + TNFa, MMP8 + MMP9 + P.gingivalis, MMP9 + P.gingivalis + IL13, MMP9 + P.gingivalis + IL10, MMP8 + P.gingivalis + IL4, MMP9 + P.gingivalis + IL4, MMP9 + T.forsythia + IL2, MMP9 + T.forsythia + IL10, MMP8 + P.gingivalis + IL13, MMP8 + MMP9 + T.forsythia, Calprotectin + T.denticola + IL6, MMP9 + T.forsythia + IL6, MMP8 + T.forsythia + IL6, Calprotectin + OPG + T.forsythia, Calprotectin + T.forsythia + ICTP, Calprotectin + T.forsythia + IL13, MMP8 + T.forsythia + IL2, MMP8 + T.forsythia + IL10, T.denticola + IL6 + IL13, MMP8 + P.gingivalis + IL2, Calprotectin + T.denticola + IL13, OPG + T.denticola + IL6, Calprotectin + T.forsythia + IL6, T.forsythia + IL6 + IL13, Calprotectin + T.denticola + IL10, Calprotectin + P.gingivalis + IL6, Calprotectin + T.denticola + IL2, MMP9 + P.gingivalis + IL2, T.forsythia + ICTP + IL13, T.denticola + IL10 + IL13, Calprotectin + P.gingivalis + ICTP, P.gingivalis + IL6 + ICTP, OPG + T.denticola + IL13, Calprotectin + T.denticola + IL4, OPG + T.denticola + IL10, Calprotectin + T.denticola + TNFa, T.denticola + IL6 + IL2, T.forsythia + IL6 + ICTP, Calprotectin + OPG + P.gingivalis, T.denticola + IL6 + TNFa, Calprotectin + T.denticola + IL1beta, OPG + T.denticola + TNFa, Calprotectin + T.forsythia + TNFa, T.denticola + IL6 + IL1beta, T.denticola + IL6 + IL4, Calprotectin + T.forsythia + IL1beta, OPG + T.denticola + IL2, OPG + T.denticola + IL1beta, T.forsythia + ICTP + TNFa, T.denticola + IL2 + IL13, T.denticola + IL6 + IL10, T.denticola + IL1beta + IL13, Calprotectin + P.gingivalis + IL10, OPG + T.forsythia + ICTP, Calprotectin + T.forsythia + IL4, OPG + T.denticola + IL4, T.forsythia + IL10 + IL13, T.denticola + IL13 + IL4, Calprotectin + T.forsythia + IL10, Calprotectin + P.gingivalis + IL2, P.gingivalis + IL6 + IL13, T.denticola + IL10 + IL2, OPG

+ T.forsythia + IL13, T.forsythia + ICTP + IL1beta, T.denticola + IL2 + TNFa, Calprotectin + T.forsythia + IL2, Calprotectin + P.gingivalis + IL13, T.denticola + IL10 + TNFa, T.denticola + IL13 + TNFa, Calprotectin + P.gingivalis + IL1beta, Calprotectin + P.gingivalis + IL4, T.forsythia + IL13 + TNFa, T.forsythia + ICTP + IL4, P.gingivalis + ICTP + IL10, T.forsythia + IL13 + IL4, T.forsythia + IL2 + IL13, OPG + P.gingivalis + IL6, T.forsythia + ICTP + IL10, T.denticola + IL1beta + IL10, T.denticola + IL10 + IL4, Calprotectin + P.gingivalis + TNFa, T.forsythia + IL6 + TNFa, T.forsythia + ICTP + IL2, T.forsythia + IL1beta + IL13, T.denticola + IL2 + IL4, T.denticola + IL1beta + IL2, OPG + T.forsythia + IL6, P.gingivalis + ICTP + IL1beta, P.gingivalis + IL6 + TNFa, T.forsythia + IL6 + IL1beta, P.gingivalis + IL6 + IL2, P.gingivalis + ICTP + IL4, P.gingivalis + ICTP + IL2, MMP8 + Calprotectin + P.intermedia, T.forsythia + IL6 + IL10, OPG + P.gingivalis + ICTP, P.gingivalis + IL6 + IL10, T.forsythia + IL6 + IL4, P.gingivalis + IL6 + IL1beta, T.denticola + IL4 + TNFa, OPG + T.forsythia + TNFa, Calprotectin + MMP9 + P.intermedia, P.gingivalis + IL6 + IL4, MMP8 + ICTP + P.intermedia, P.gingivalis + ICTP + IL13, P.gingivalis + ICTP + TNFa, T.forsythia + IL6 + IL2, T.denticola + IL1beta + IL4, MMP8 + TNFa + P.intermedia, OPG + T.forsythia + IL1beta, OPG + T.forsythia + IL4, T.denticola + IL1beta + TNFa, OPG + T.forsythia + IL10, OPG + T.forsythia + IL2, MMP9 + TNFa + P.intermedia, T.forsythia + IL2 + TNFa, T.forsythia + IL4 + TNFa, T.forsythia + IL1beta + TNFa, P.gingivalis + IL10 + IL13, MMP8 + IL1beta + P.intermedia, OPG + P.gingivalis + IL10, T.forsythia + IL10 + TNFa, MMP8 + IL6 + P.intermedia, OPG + P.gingivalis + IL1beta, MMP8 + OPG + P.intermedia, OPG + P.gingivalis + IL4, P.gingivalis + IL10 + IL2, T.forsythia + IL1beta + IL4, OPG + P.gingivalis + IL2, T.forsythia + IL2 + IL4, T.forsythia + IL1beta + IL10, MMP9 + ICTP + P.intermedia, P.gingivalis + IL1beta + IL10, P.gingivalis + IL2 + IL13, T.forsythia + IL1beta + IL2, OPG + P.gingivalis + TNFa, MMP8 + MMP9 + P.intermedia, P.gingivalis + IL1beta + IL2, P.gingivalis + IL10 + IL4, T.forsythia + IL10 + IL4, OPG + P.gingivalis + IL13, MMP8 + IL13 + P.intermedia, P.gingivalis + IL10 + TNFa, P.gingivalis + IL13 + TNFa, P.gingivalis + IL13 + IL4, MMP8 + IL4 + P.intermedia, MMP8 + IL10 + P.intermedia, P.gingivalis + IL2 + IL4, P.gingivalis + IL2 + TNFa, T.forsythia + IL10 + IL2, MMP8 + IL2 + P.intermedia, MMP9 + IL1beta + P.intermedia, P.gingivalis + IL1beta + IL4, Calprotectin + TNFa + P.intermedia, MMP9 + IL2 + P.intermedia, P.gingivalis + IL1beta + IL13, MMP9 + IL6 + P.intermedia, Calprotectin + MMP9 + C.rectus, P.gingivalis + IL1beta + TNFa, MMP9 + OPG + P.intermedia, P.gingivalis + IL4 + TNFa, Calprotectin + ICTP + P.intermedia, Calprotectin + OPG + P.intermedia, MMP9 + IL13 + P.intermedia, Calprotectin + IL13 + P.intermedia, MMP9 + IL10 + P.intermedia, Calprotectin + IL2 + P.intermedia, MMP8 + Calprotectin + C.rectus, Calprotectin + IL6 +

P.intermedia, Calprotectin + IL1beta + P.intermedia, MMP9 + IL4 + P.intermedia,
 Calprotectin + IL10 + P.intermedia, Calprotectin + IL4 + P.intermedia, MMP8 + ICTP +
 C.rectus, MMP9 + ICTP + C.rectus, ICTP + TNFa + P.intermedia, MMP9 + TNFa +
 C.rectus, Calprotectin + MMP9 + F.nucleatum, MMP9 + IL6 + C.rectus, IL4 + TNFa +
 P.intermedia, IL6 + ICTP + P.intermedia, MMP8 + MMP9 + C.rectus, ICTP + IL4 +
 P.intermedia, ICTP + IL1beta + P.intermedia, MMP8 + TNFa + C.rectus, MMP9 + OPG +
 C.rectus, MMP9 + IL1beta + C.rectus, IL1beta + TNFa + P.intermedia, MMP9 + IL10 +
 C.rectus, ICTP + IL13 + P.intermedia, IL6 + TNFa + P.intermedia, MMP8 + IL10 + C.rectus,
 IL2 + TNFa + P.intermedia, MMP9 + IL2 + C.rectus, ICTP + IL2 + P.intermedia, MMP9 +
 IL13 + C.rectus, MMP9 + IL4 + C.rectus, ICTP + IL10 + P.intermedia, IL10 + TNFa +
 P.intermedia, Calprotectin + OPG + C.rectus, MMP8 + ICTP + F.nucleatum, OPG + ICTP +
 P.intermedia, MMP8 + IL6 + C.rectus, MMP8 + IL1beta + C.rectus, MMP8 + Calprotectin +
 F.nucleatum, MMP8 + IL13 + C.rectus, MMP8 + IL4 + C.rectus, OPG + TNFa +
 P.intermedia, MMP8 + OPG + C.rectus, IL13 + TNFa + P.intermedia, MMP8 + IL2 +
 C.rectus, Calprotectin + IL6 + C.rectus, IL13 + IL4 + P.intermedia, MMP9 + TNFa +
 F.nucleatum, IL1beta + IL13 + P.intermedia, IL6 + IL13 + P.intermedia, MMP8 + TNFa +
 F.nucleatum, MMP9 + ICTP + F.nucleatum, Calprotectin + IL10 + C.rectus, IL6 + IL4 +
 P.intermedia, IL6 + IL1beta + P.intermedia, IL10 + IL13 + P.intermedia, OPG + IL4 +
 P.intermedia, IL10 + IL4 + P.intermedia, IL1beta + IL4 + P.intermedia, Calprotectin + ICTP
 + C.rectus, IL2 + IL13 + P.intermedia, OPG + IL1beta + P.intermedia, MMP8 + IL10 +
 F.nucleatum, OPG + IL13 + P.intermedia, MMP9 + IL10 + F.nucleatum, IL1beta + IL10 +
 P.intermedia, IL2 + IL4 + P.intermedia, MMP8 + OPG + F.nucleatum, MMP8 + IL1beta +
 F.nucleatum, IL1beta + IL2 + P.intermedia, MMP8 + IL4 + F.nucleatum, MMP9 + IL1beta +
 F.nucleatum, OPG + IL2 + P.intermedia, IL6 + IL2 + P.intermedia, MMP9 + IL4 +
 F.nucleatum, OPG + IL10 + P.intermedia, Calprotectin + IL1beta + C.rectus, MMP8 + IL2 +
 F.nucleatum, Calprotectin + IL4 + C.rectus, MMP8 + IL6 + F.nucleatum, MMP9 + OPG +
 F.nucleatum, OPG + IL6 + P.intermedia, IL10 + IL2 + P.intermedia, IL6 + IL10 +
 P.intermedia, MMP8 + MMP9 + F.nucleatum, MMP8 + IL13 + F.nucleatum, MMP9 + IL6 +
 F.nucleatum, MMP9 + IL13 + F.nucleatum, MMP9 + IL2 + F.nucleatum, IL6 + ICTP +
 C.rectus, Calprotectin + OPG + F.nucleatum, Calprotectin + IL13 + C.rectus, Calprotectin +
 TNFa + C.rectus, Calprotectin + IL2 + C.rectus, Calprotectin + IL6 + F.nucleatum,
 Calprotectin + ICTP + F.nucleatum, IL6 + IL4 + C.rectus, Calprotectin + TNFa +
 F.nucleatum, ICTP + IL1beta + C.rectus, Calprotectin + IL10 + F.nucleatum, IL6 + ICTP +
 F.nucleatum, ICTP + IL4 + C.rectus, Calprotectin + IL4 + F.nucleatum, IL6 + IL13 +
 C.rectus, IL6 + TNFa + C.rectus, IL6 + IL1beta + C.rectus, IL4 + TNFa + C.rectus,

Calprotectin + IL2 + F.nucleatum, OPG + IL6 + C.rectus, IL4 + TNFa + F.nucleatum, ICTP + IL10 + C.rectus, IL6 + IL2 + C.rectus, IL6 + IL10 + C.rectus, ICTP + IL13 + C.rectus, Calprotectin + IL13 + F.nucleatum, ICTP + TNFa + C.rectus, ICTP + IL2 + C.rectus, OPG + ICTP + C.rectus, IL6 + TNFa + F.nucleatum, Calprotectin + IL1beta + F.nucleatum, ICTP + IL4 + F.nucleatum, IL10 + IL4 + C.rectus, ICTP + IL10 + F.nucleatum, OPG + IL6 + F.nucleatum, OPG + IL4 + C.rectus, IL13 + IL4 + C.rectus, IL6 + IL10 + F.nucleatum, IL2 + IL4 + C.rectus, IL1beta + IL4 + C.rectus, OPG + IL10 + C.rectus, IL1beta + IL10 + C.rectus, IL10 + TNFa + C.rectus, ICTP + IL1beta + F.nucleatum, ICTP + TNFa + F.nucleatum, OPG + IL1beta + C.rectus, IL1beta + TNFa + C.rectus, IL10 + IL2 + C.rectus, IL10 + IL13 + C.rectus, IL6 + IL13 + F.nucleatum, IL6 + IL4 + F.nucleatum, OPG + ICTP + F.nucleatum, IL1beta + IL2 + C.rectus, IL6 + IL1beta + F.nucleatum, IL1beta + IL13 + C.rectus, IL10 + TNFa + F.nucleatum, OPG + TNFa + C.rectus, ICTP + IL13 + F.nucleatum, IL13 + IL4 + F.nucleatum, OPG + IL4 + F.nucleatum, IL2 + TNFa + C.rectus, IL13 + TNFa + C.rectus, ICTP + IL2 + F.nucleatum, OPG + IL10 + F.nucleatum, IL10 + IL4 + F.nucleatum, IL2 + IL13 + C.rectus, OPG + IL13 + C.rectus, OPG + IL2 + C.rectus, IL6 + IL2 + F.nucleatum, IL10 + IL13 + F.nucleatum, IL2 + IL4 + F.nucleatum, IL1beta + IL4 + F.nucleatum, IL1beta + IL10 + F.nucleatum, IL1beta + TNFa + F.nucleatum, OPG + TNFa + F.nucleatum, IL10 + IL2 + F.nucleatum, OPG + IL1beta + F.nucleatum, OPG + IL13 + F.nucleatum, OPG + IL2 + F.nucleatum, IL1beta + IL13 + F.nucleatum, IL1beta + IL2 + F.nucleatum, IL2 + TNFa + F.nucleatum, IL13 + TNFa + F.nucleatum, IL2 + IL13 + F.nucleatum, MMP8 + T.denticola + ICTP + C.rectus, MMP8 + T.denticola + ICTP + P.intermedia, MMP9 + T.denticola + ICTP + C.rectus, Calprotectin + T.denticola + ICTP + C.rectus, T.denticola + IL6 + ICTP + C.rectus, MMP8 + T.forsythia + T.denticola + ICTP, MMP9 + T.denticola + ICTP + P.intermedia, MMP8 + P.gingivalis + T.denticola + ICTP, MMP8 + T.denticola + IL1beta + P.intermedia, MMP9 + T.forsythia + T.denticola + ICTP, MMP8 + Calprotectin + P.gingivalis + P.intermedia, Calprotectin + MMP9 + T.denticola + C.rectus, T.denticola + ICTP + IL10 + C.rectus, T.forsythia + T.denticola + ICTP + IL13, MMP8 + T.denticola + TNFa + P.intermedia, MMP8 + Calprotectin + T.denticola + P.intermedia, MMP9 + P.gingivalis + T.denticola + ICTP, Calprotectin + MMP9 + P.gingivalis + P.intermedia, Calprotectin + T.denticola + ICTP + P.intermedia, T.denticola + ICTP + TNFa + P.intermedia, MMP8 + T.denticola + ICTP + F.nucleatum, MMP8 + OPG + T.denticola + P.intermedia, MMP8 + T.denticola + IL13 + P.intermedia, T.denticola + ICTP + IL13 + P.intermedia, T.forsythia + T.denticola + IL6 + ICTP, T.denticola + ICTP + IL2 + C.rectus, MMP8 + T.denticola + IL4 + P.intermedia, T.denticola + IL6 + ICTP + P.intermedia, MMP9 + T.denticola + TNFa + P.intermedia, T.denticola + ICTP + IL1beta + C.rectus, Calprotectin

+ MMP9 + T.denticola + P.intermedia, T.denticola + ICTP + IL1beta + P.intermedia, OPG + T.denticola + ICTP + C.rectus, T.denticola + ICTP + IL4 + C.rectus, MMP8 + P.gingivalis + ICTP + P.intermedia, MMP8 + T.forsythia + IL1beta + P.intermedia, T.denticola + ICTP + IL4 + P.intermedia, T.denticola + ICTP + IL13 + C.rectus, MMP9 + T.denticola + IL1beta + P.intermedia, OPG + T.denticola + ICTP + P.intermedia, OPG + T.forsythia + T.denticola + ICTP, MMP8 + Calprotectin + T.denticola + C.rectus, MMP8 + OPG + T.denticola + C.rectus, MMP9 + T.denticola + IL13 + P.intermedia, T.denticola + ICTP + IL10 + P.intermedia, T.denticola + ICTP + TNFa + C.rectus, MMP8 + Calprotectin + T.forsythia + P.intermedia, MMP8 + T.denticola + IL6 + P.intermedia, MMP9 + T.denticola + IL1beta + C.rectus, P.gingivalis + T.denticola + IL6 + ICTP, MMP8 + T.denticola + IL1beta + C.rectus, T.denticola + ICTP + IL2 + P.intermedia, MMP8 + P.gingivalis + IL1beta + P.intermedia, MMP8 + T.forsythia + T.denticola + IL1beta, T.forsythia + T.denticola + ICTP + TNFa, MMP8 + T.forsythia + TNFa + P.intermedia, MMP9 + OPG + T.denticola + C.rectus, T.forsythia + T.denticola + ICTP + IL1beta, Calprotectin + T.forsythia + T.denticola + ICTP, MMP8 + MMP9 + T.denticola + P.intermedia, MMP8 + T.denticola + IL2 + P.intermedia, MMP9 + T.denticola + ICTP + F.nucleatum, Calprotectin + MMP9 + T.forsythia + P.intermedia, MMP9 + OPG + T.denticola + P.intermedia, MMP9 + T.denticola + IL4 + P.intermedia, T.forsythia + T.denticola + ICTP + IL10, MMP8 + T.forsythia + ICTP + P.intermedia, T.forsythia + T.denticola + ICTP + IL4, MMP8 + P.gingivalis + TNFa + P.intermedia, Calprotectin + MMP9 + P.gingivalis + T.denticola, Calprotectin + OPG + T.denticola + C.rectus, T.forsythia + T.denticola + ICTP + IL2, MMP8 + T.denticola + IL10 + P.intermedia, MMP9 + T.forsythia + T.denticola + IL1beta, MMP8 + T.forsythia + IL13 + P.intermedia, Calprotectin + MMP9 + T.forsythia + T.denticola, Calprotectin + T.denticola + IL6 + C.rectus, MMP9 + T.denticola + TNFa + C.rectus, MMP8 + Calprotectin + T.forsythia + T.denticola, Calprotectin + T.denticola + IL13 + P.intermedia, MMP8 + MMP9 + T.denticola + C.rectus, MMP8 + OPG + T.forsythia + T.denticola, Calprotectin + T.denticola + TNFa + P.intermedia, MMP8 + P.gingivalis + T.denticola + IL1beta, MMP8 + T.forsythia + T.denticola + IL13, MMP9 + T.forsythia + T.denticola + IL13, MMP9 + T.forsythia + TNFa + P.intermedia, MMP9 + T.denticola + IL6 + C.rectus, OPG + P.gingivalis + T.denticola + ICTP, Calprotectin + OPG + T.denticola + P.intermedia, P.gingivalis + T.denticola + ICTP + IL10, MMP8 + P.gingivalis + IL13 + P.intermedia, MMP8 + P.gingivalis + IL4 + P.intermedia, MMP8 + T.denticola + IL4 + C.rectus, MMP8 + T.denticola + TNFa + C.rectus, MMP9 + OPG + T.forsythia + T.denticola, MMP9 + T.denticola + IL6 + P.intermedia, MMP9 + T.denticola + IL2 + P.intermedia, MMP8 + Calprotectin + P.gingivalis + T.denticola, MMP9 + P.gingivalis + ICTP + P.intermedia,

MMP9 + T.forsythia + T.denticola + TNFa, MMP8 + T.forsythia + IL4 + P.intermedia,
 MMP9 + P.gingivalis + T.denticola + IL13, MMP9 + T.denticola + IL4 + C.rectus,
 T.denticola + IL6 + ICTP + F.nucleatum, MMP8 + T.forsythia + T.denticola + TNFa, MMP8
 + T.denticola + IL10 + C.rectus, Calprotectin + P.gingivalis + T.denticola + ICTP,
 Calprotectin + T.denticola + ICTP + F.nucleatum, Calprotectin + T.denticola + IL4 +
 P.intermedia, P.gingivalis + T.denticola + ICTP + IL13, MMP8 + P.gingivalis + T.denticola
 + IL13, Calprotectin + P.gingivalis + ICTP + P.intermedia, MMP9 + T.denticola + IL10 +
 C.rectus, MMP9 + P.gingivalis + IL1beta + P.intermedia, MMP8 + OPG + P.gingivalis +
 T.denticola, MMP8 + T.denticola + IL6 + C.rectus, MMP9 + OPG + P.gingivalis +
 T.denticola, MMP9 + P.gingivalis + T.denticola + IL1beta, MMP9 + T.forsythia + IL13 +
 P.intermedia, MMP8 + T.denticola + IL13 + C.rectus, Calprotectin + T.denticola + IL10 +
 C.rectus, MMP8 + OPG + T.forsythia + P.intermedia, MMP8 + T.forsythia + T.denticola +
 IL4, MMP9 + T.forsythia + T.denticola + IL4, MMP9 + T.denticola + IL2 + C.rectus, MMP9
 + T.denticola + IL13 + C.rectus, OPG + T.denticola + IL13 + P.intermedia, MMP8 + OPG +
 P.gingivalis + P.intermedia, MMP9 + T.forsythia + IL1beta + P.intermedia, MMP9 +
 T.denticola + IL10 + P.intermedia, MMP8 + T.denticola + IL2 + C.rectus, Calprotectin +
 T.forsythia + T.denticola + IL13, P.gingivalis + T.denticola + ICTP + TNFa, MMP8 +
 P.gingivalis + T.denticola + IL4, MMP8 + P.gingivalis + IL2 + P.intermedia, Calprotectin +
 T.denticola + IL6 + P.intermedia, Calprotectin + T.denticola + IL1beta + P.intermedia,
 MMP9 + P.gingivalis + T.denticola + IL4, P.gingivalis + T.denticola + ICTP + IL2,
 P.gingivalis + T.denticola + ICTP + IL4, T.denticola + IL2 + IL13 + P.intermedia, OPG +
 T.denticola + ICTP + F.nucleatum, T.denticola + ICTP + IL10 + F.nucleatum, T.denticola +
 IL1beta + IL13 + P.intermedia, MMP8 + T.forsythia + IL10 + P.intermedia, T.denticola +
 ICTP + IL2 + F.nucleatum, MMP8 + T.forsythia + IL6 + P.intermedia, MMP9 + P.gingivalis
 + T.denticola + TNFa, MMP9 + P.gingivalis + IL13 + P.intermedia, MMP9 + T.forsythia +
 ICTP + P.intermedia, MMP8 + MMP9 + P.gingivalis + T.denticola, MMP8 + P.gingivalis +
 IL6 + P.intermedia, Calprotectin + T.forsythia + ICTP + P.intermedia, Calprotectin +
 T.forsythia + IL13 + P.intermedia, MMP9 + P.gingivalis + IL4 + P.intermedia, MMP9 +
 P.gingivalis + TNFa + P.intermedia, T.denticola + IL10 + IL13 + P.intermedia, MMP8 +
 P.gingivalis + T.forsythia + ICTP, MMP8 + P.gingivalis + T.denticola + TNFa, Calprotectin
 + MMP9 + T.forsythia + C.rectus, Calprotectin + T.denticola + IL10 + P.intermedia, MMP8
 + P.gingivalis + T.denticola + IL2, MMP8 + MMP9 + T.forsythia + T.denticola, Calprotectin
 + MMP9 + P.gingivalis + T.forsythia, MMP9 + P.gingivalis + T.forsythia + ICTP,
 P.gingivalis + T.denticola + ICTP + IL1beta, T.denticola + IL6 + IL13 + P.intermedia,
 T.denticola + ICTP + IL13 + F.nucleatum, MMP8 + Calprotectin + T.denticola +

F.nucleatum, MMP8 + P.gingivalis + IL10 + P.intermedia, MMP8 + Calprotectin + P.gingivalis + T.forsythia, MMP8 + OPG + T.denticola + F.nucleatum, MMP8 + T.forsythia + T.denticola + IL2, Calprotectin + T.denticola + IL2 + P.intermedia, Calprotectin + T.denticola + IL13 + C.rectus, MMP9 + T.forsythia + IL4 + P.intermedia, T.denticola + IL13 + IL4 + P.intermedia, MMP8 + T.forsythia + IL2 + P.intermedia, Calprotectin + MMP9 + T.denticola + F.nucleatum, T.denticola + ICTP + TNFa + F.nucleatum, T.denticola + IL13 + TNFa + P.intermedia, Calprotectin + MMP9 + P.gingivalis + C.rectus, MMP9 + T.forsythia + T.denticola + IL10, MMP9 + T.forsythia + IL2 + P.intermedia, MMP8 + MMP9 + P.gingivalis + P.intermedia, Calprotectin + T.denticola + IL2 + C.rectus, Calprotectin + T.denticola + TNFa + C.rectus, OPG + T.denticola + IL4 + P.intermedia, T.denticola + ICTP + IL4 + F.nucleatum, T.denticola + ICTP + IL1beta + F.nucleatum, MMP8 + P.gingivalis + T.denticola + IL10, Calprotectin + OPG + P.gingivalis + P.intermedia, Calprotectin + P.gingivalis + TNFa + P.intermedia, MMP9 + T.forsythia + T.denticola + IL6, MMP9 + T.forsythia + IL10 + P.intermedia, Calprotectin + T.denticola + IL4 + C.rectus, OPG + T.denticola + TNFa + P.intermedia, MMP8 + T.forsythia + T.denticola + IL6, MMP8 + T.forsythia + T.denticola + IL10, MMP8 + T.forsythia + ICTP + C.rectus, MMP8 + T.denticola + IL1beta + F.nucleatum, Calprotectin + P.gingivalis + IL4 + P.intermedia, MMP9 + P.gingivalis + T.denticola + IL6, Calprotectin + P.gingivalis + IL13 + P.intermedia, MMP9 + OPG + P.gingivalis + P.intermedia, MMP9 + P.gingivalis + IL2 + P.intermedia, T.denticola + IL6 + TNFa + P.intermedia, T.denticola + IL2 + TNFa + P.intermedia, MMP9 + OPG + T.denticola + F.nucleatum, OPG + T.denticola + IL6 + P.intermedia, OPG + T.denticola + IL1beta + P.intermedia, Calprotectin + OPG + T.forsythia + P.intermedia, Calprotectin + T.denticola + IL1beta + C.rectus, MMP9 + OPG + T.forsythia + P.intermedia, MMP9 + P.gingivalis + T.forsythia + IL13, T.denticola + IL10 + TNFa + P.intermedia, Calprotectin + OPG + T.forsythia + C.rectus, Calprotectin + P.gingivalis + IL10 + P.intermedia, Calprotectin + T.forsythia + TNFa + P.intermedia, T.denticola + IL6 + IL4 + P.intermedia, T.denticola + IL2 + IL4 + P.intermedia, MMP9 + P.gingivalis + T.denticola + IL2, MMP9 + T.denticola + IL1beta + F.nucleatum, T.forsythia + T.denticola + IL6 + IL13, Calprotectin + P.gingivalis + IL1beta + P.intermedia, MMP9 + P.gingivalis + T.forsythia + TNFa, T.denticola + IL6 + IL13 + C.rectus, MMP8 + P.gingivalis + T.forsythia + IL1beta, MMP8 + P.gingivalis + T.forsythia + TNFa, T.denticola + IL6 + IL2 + P.intermedia, T.denticola + IL10 + IL4 + P.intermedia, MMP8 + MMP9 + T.forsythia + P.intermedia, MMP9 + P.gingivalis + T.forsythia + IL1beta, MMP9 + T.forsythia + T.denticola + IL2, MMP8 + P.gingivalis + T.forsythia + IL4, MMP8 + P.gingivalis + T.denticola + IL6, MMP8 + T.forsythia + IL1beta + C.rectus, Calprotectin + P.gingivalis + IL2 + P.intermedia,

Calprotectin + T.forsythia + IL1beta + P.intermedia, MMP9 + P.gingivalis + T.forsythia + IL4, MMP9 + P.gingivalis + IL6 + P.intermedia, MMP8 + P.gingivalis + T.forsythia + IL13, Calprotectin + OPG + T.forsythia + T.denticola, MMP8 + T.forsythia + IL1beta + F.nucleatum, MMP9 + OPG + P.gingivalis + T.forsythia, MMP9 + P.gingivalis + T.denticola + IL10, MMP9 + T.forsythia + ICTP + C.rectus, MMP8 + P.gingivalis + ICTP + F.nucleatum, Calprotectin + P.gingivalis + IL6 + P.intermedia, Calprotectin + T.forsythia + IL4 + P.intermedia, Calprotectin + MMP9 + T.forsythia + F.nucleatum, Calprotectin + T.forsythia + IL10 + P.intermedia, MMP9 + T.forsythia + IL6 + P.intermedia, OPG + T.denticola + IL6 + C.rectus, T.forsythia + T.denticola + IL10 + IL13, T.forsythia + ICTP + IL13 + P.intermedia, T.denticola + IL6 + IL1beta + P.intermedia, T.denticola + IL6 + TNFa + C.rectus, T.denticola + IL1beta + TNFa + P.intermedia, T.denticola + IL4 + TNFa + P.intermedia, Calprotectin + MMP9 + P.gingivalis + F.nucleatum, MMP8 + OPG + P.gingivalis + T.forsythia, MMP8 + T.denticola + IL2 + F.nucleatum, OPG + T.denticola + IL10 + P.intermedia, T.denticola + IL1beta + IL2 + P.intermedia, MMP9 + P.gingivalis + IL10 + P.intermedia, MMP9 + T.denticola + IL10 + F.nucleatum, OPG + T.denticola + IL2 + P.intermedia, T.denticola + IL6 + IL4 + C.rectus, T.denticola + IL1beta + IL4 + P.intermedia, MMP8 + Calprotectin + P.gingivalis + C.rectus, MMP8 + Calprotectin + T.forsythia + F.nucleatum, MMP8 + T.forsythia + ICTP + F.nucleatum, MMP8 + T.denticola + IL10 + F.nucleatum, Calprotectin + T.forsythia + IL2 + P.intermedia, MMP9 + T.forsythia + IL1beta + C.rectus, OPG + T.denticola + IL10 + C.rectus, MMP8 + Calprotectin + T.forsythia + C.rectus, Calprotectin + T.forsythia + IL6 + P.intermedia, Calprotectin + T.forsythia + IL6 + C.rectus, T.forsythia + IL13 + TNFa + P.intermedia, T.denticola + IL1beta + IL10 + P.intermedia, T.denticola + IL6 + IL2 + C.rectus, MMP8 + MMP9 + P.gingivalis + T.forsythia, T.denticola + IL6 + IL1beta + C.rectus, MMP9 + T.forsythia + IL1beta + F.nucleatum, OPG + T.forsythia + T.denticola + IL13, T.forsythia + ICTP + IL1beta + P.intermedia, MMP9 + T.denticola + IL2 + F.nucleatum, P.gingivalis + IL6 + ICTP + P.intermedia, T.forsythia + ICTP + TNFa + P.intermedia, T.denticola + IL6 + IL10 + P.intermedia, T.denticola + IL6 + IL10 + C.rectus, MMP9 + T.denticola + TNFa + F.nucleatum, T.forsythia + ICTP + IL4 + P.intermedia, MMP8 + T.denticola + IL13 + F.nucleatum, MMP8 + T.denticola + TNFa + F.nucleatum, MMP8 + MMP9 + T.denticola + F.nucleatum, Calprotectin + T.forsythia + ICTP + C.rectus, MMP9 + T.denticola + IL6 + F.nucleatum, MMP9 + T.denticola + IL13 + F.nucleatum, MMP9 + T.denticola + IL4 + F.nucleatum, MMP8 + P.gingivalis + ICTP + C.rectus, OPG + T.denticola + IL13 + C.rectus, T.denticola + IL10 + IL2 + P.intermedia, T.denticola + IL10 + IL13 + C.rectus, MMP8 + T.denticola + IL6 + F.nucleatum, Calprotectin + OPG + T.denticola + F.nucleatum, OPG +

T.forsythia + T.denticola + TNFa, T.forsythia + T.denticola + IL2 + IL13, T.forsythia + IL6 + IL13 + P.intermedia, MMP9 + P.gingivalis + ICTP + C.rectus, T.forsythia + IL10 + IL13 + P.intermedia, T.denticola + IL10 + IL2 + C.rectus, MMP8 + T.denticola + IL4 + F.nucleatum, Calprotectin + OPG + T.forsythia + F.nucleatum, MMP9 + P.gingivalis + T.forsythia + IL2, MMP8 + T.forsythia + TNFa + C.rectus, MMP8 + Calprotectin + P.gingivalis + F.nucleatum, MMP9 + T.forsythia + ICTP + F.nucleatum, MMP9 + T.forsythia + IL2 + C.rectus, OPG + T.forsythia + T.denticola + IL4, T.forsythia + ICTP + IL10 + P.intermedia, Calprotectin + P.gingivalis + T.forsythia + IL13, OPG + T.forsythia + T.denticola + IL6, MMP9 + P.gingivalis + T.forsythia + IL10, MMP8 + OPG + T.forsythia + C.rectus, Calprotectin + T.forsythia + T.denticola + IL6, MMP9 + P.gingivalis + ICTP + F.nucleatum, MMP9 + T.forsythia + TNFa + F.nucleatum, T.forsythia + ICTP + IL2 + P.intermedia, T.denticola + IL1beta + IL10 + C.rectus, T.denticola + IL10 + IL4 + C.rectus, MMP8 + P.gingivalis + T.forsythia + IL10, Calprotectin + P.gingivalis + IL6 + C.rectus, Calprotectin + T.forsythia + T.denticola + IL10, MMP9 + OPG + T.forsythia + C.rectus, OPG + T.forsythia + T.denticola + IL1beta, T.forsythia + IL1beta + IL13 + P.intermedia, T.forsythia + IL2 + IL13 + P.intermedia, T.denticola + IL10 + TNFa + C.rectus, MMP8 + T.forsythia + TNFa + F.nucleatum, Calprotectin + T.forsythia + T.denticola + TNFa, Calprotectin + T.forsythia + ICTP + F.nucleatum, P.gingivalis + ICTP + IL13 + P.intermedia, P.gingivalis + IL10 + IL13 + P.intermedia, MMP9 + P.gingivalis + T.forsythia + IL6, OPG + T.forsythia + T.denticola + IL10, MMP8 + P.gingivalis + T.forsythia + IL6, Calprotectin + T.forsythia + T.denticola + IL1beta, OPG + T.forsythia + T.denticola + IL2, P.gingivalis + ICTP + IL1beta + P.intermedia, T.denticola + IL1beta + IL13 + C.rectus, Calprotectin + T.forsythia + T.denticola + IL2, P.gingivalis + ICTP + TNFa + P.intermedia, MMP9 + T.forsythia + IL4 + C.rectus, T.forsythia + IL6 + ICTP + P.intermedia, T.denticola + IL2 + IL13 + C.rectus, MMP9 + T.forsythia + IL13 + F.nucleatum, MMP9 + T.forsythia + IL13 + C.rectus, OPG + T.forsythia + ICTP + P.intermedia, MMP8 + P.gingivalis + T.forsythia + IL2, OPG + T.forsythia + IL13 + P.intermedia, T.forsythia + T.denticola + IL13 + IL4, T.denticola + IL2 + TNFa + C.rectus, P.gingivalis + ICTP + IL10 + P.intermedia, T.forsythia + T.denticola + IL1beta + IL13, T.forsythia + IL13 + IL4 + P.intermedia, P.gingivalis + IL1beta + IL13 + P.intermedia, MMP8 + T.forsythia + IL13 + F.nucleatum, Calprotectin + P.gingivalis + T.forsythia + ICTP, T.forsythia + T.denticola + IL2 + TNFa, MMP8 + MMP9 + T.forsythia + C.rectus, MMP8 + T.forsythia + IL13 + C.rectus, Calprotectin + T.forsythia + T.denticola + IL4, Calprotectin + T.forsythia + IL13 + F.nucleatum, OPG + T.denticola + IL1beta + C.rectus, T.denticola + IL1beta + IL2 + C.rectus, T.denticola + IL2 + IL4 + C.rectus, MMP8 + OPG + T.forsythia + F.nucleatum, MMP8 + T.forsythia + IL4 + C.rectus,

Calprotectin + OPG + P.gingivalis + T.denticola, OPG + T.denticola + IL2 + C.rectus,
 T.forsythia + IL1beta + TNFa + P.intermedia, P.gingivalis + ICTP + IL2 + P.intermedia,
 T.forsythia + IL10 + TNFa + P.intermedia, Calprotectin + P.gingivalis + T.denticola + IL13,
 Calprotectin + T.forsythia + IL1beta + F.nucleatum, OPG + P.gingivalis + ICTP +
 P.intermedia, P.gingivalis + ICTP + IL4 + P.intermedia, T.forsythia + T.denticola + IL1beta
 + IL10, T.forsythia + T.denticola + IL10 + TNFa, MMP8 + T.forsythia + IL2 + C.rectus,
 Calprotectin + T.forsythia + IL13 + C.rectus, T.forsythia + T.denticola + IL6 + IL4,
 T.forsythia + IL6 + TNFa + P.intermedia, Calprotectin + OPG + P.gingivalis + T.forsythia,
 T.forsythia + T.denticola + IL6 + TNFa, T.forsythia + T.denticola + IL13 + TNFa,
 T.denticola + IL13 + IL4 + C.rectus, MMP9 + T.forsythia + IL6 + C.rectus, OPG +
 P.gingivalis + T.denticola + IL13, OPG + T.forsythia + TNFa + P.intermedia, P.gingivalis +
 T.forsythia + IL6 + ICTP, T.forsythia + T.denticola + IL6 + IL1beta, Calprotectin +
 P.gingivalis + T.denticola + IL6, OPG + P.gingivalis + T.denticola + IL10, T.forsythia +
 T.denticola + IL1beta + IL2, MMP9 + T.forsythia + TNFa + C.rectus, Calprotectin +
 P.gingivalis + ICTP + F.nucleatum, MMP9 + T.forsythia + IL10 + C.rectus, OPG +
 T.denticola + IL4 + C.rectus, T.forsythia + T.denticola + IL2 + IL4, OPG + P.gingivalis +
 T.denticola + IL6, OPG + T.denticola + TNFa + C.rectus, P.gingivalis + T.denticola + IL10 +
 IL13, T.forsythia + IL2 + TNFa + P.intermedia, T.denticola + IL13 + TNFa + C.rectus,
 T.denticola + IL4 + TNFa + C.rectus, T.forsythia + IL1beta + IL10 + P.intermedia,
 T.forsythia + IL4 + TNFa + P.intermedia, Calprotectin + OPG + P.gingivalis + C.rectus,
 T.forsythia + T.denticola + IL6 + IL2, T.forsythia + T.denticola + IL1beta + TNFa,
 T.denticola + IL1beta + IL4 + C.rectus, Calprotectin + T.denticola + IL6 + F.nucleatum,
 P.gingivalis + T.forsythia + IL6 + IL13, P.gingivalis + IL6 + IL13 + P.intermedia,
 Calprotectin + T.forsythia + TNFa + F.nucleatum, MMP9 + T.forsythia + IL4 + F.nucleatum,
 OPG + P.gingivalis + T.denticola + IL4, P.gingivalis + IL6 + TNFa + P.intermedia,
 Calprotectin + T.forsythia + IL1beta + C.rectus, MMP9 + P.gingivalis + IL6 + F.nucleatum,
 MMP9 + P.gingivalis + IL10 + F.nucleatum, P.gingivalis + T.denticola + IL6 + IL13,
 T.forsythia + T.denticola + IL1beta + IL4, T.forsythia + IL6 + IL10 + P.intermedia,
 T.forsythia + IL6 + IL13 + C.rectus, T.denticola + IL1beta + TNFa + C.rectus, MMP8 +
 P.gingivalis + IL10 + F.nucleatum, MMP8 + T.forsythia + IL10 + C.rectus, MMP9 +
 P.gingivalis + IL6 + C.rectus, MMP9 + P.gingivalis + TNFa + C.rectus, T.forsythia +
 T.denticola + IL10 + IL4, T.forsythia + IL6 + IL1beta + P.intermedia, MMP8 + T.forsythia +
 IL6 + C.rectus, Calprotectin + P.gingivalis + T.forsythia + IL6, Calprotectin + T.forsythia +
 TNFa + C.rectus, MMP9 + T.forsythia + IL2 + F.nucleatum, OPG + P.gingivalis +
 T.denticola + IL1beta, OPG + P.gingivalis + T.denticola + IL2, T.forsythia + IL6 + ICTP +

C.rectus, MMP8 + P.gingivalis + IL1beta + F.nucleatum, MMP9 + OPG + P.gingivalis +
 C.rectus, OPG + P.gingivalis + IL13 + P.intermedia, OPG + T.forsythia + IL1beta +
 P.intermedia, T.forsythia + T.denticola + IL4 + TNFa, MMP8 + MMP9 + P.gingivalis +
 C.rectus, MMP8 + T.forsythia + IL4 + F.nucleatum, Calprotectin + T.forsythia + IL10 +
 C.rectus, Calprotectin + T.denticola + IL2 + F.nucleatum, P.gingivalis + T.denticola + IL2 +
 IL13, P.gingivalis + IL13 + IL4 + P.intermedia, MMP8 + T.forsythia + IL6 + F.nucleatum,
 MMP9 + T.forsythia + IL6 + F.nucleatum, P.gingivalis + T.denticola + IL1beta + IL13,
 P.gingivalis + IL6 + IL4 + P.intermedia, T.forsythia + T.denticola + IL10 + IL2, Calprotectin
 + OPG + P.gingivalis + F.nucleatum, Calprotectin + T.forsythia + IL6 + F.nucleatum, OPG +
 T.forsythia + IL2 + P.intermedia, P.gingivalis + IL6 + ICTP + F.nucleatum, P.gingivalis +
 IL6 + IL1beta + P.intermedia, Calprotectin + T.forsythia + IL4 + F.nucleatum, MMP9 +
 P.gingivalis + IL1beta + F.nucleatum, MMP9 + P.gingivalis + IL4 + C.rectus, OPG +
 T.forsythia + IL6 + P.intermedia, T.forsythia + T.denticola + IL6 + IL10, T.forsythia + IL10
 + IL4 + P.intermedia, MMP9 + P.gingivalis + TNFa + F.nucleatum, OPG + P.gingivalis +
 T.forsythia + IL6, OPG + P.gingivalis + T.denticola + TNFa, P.gingivalis + IL2 + IL13 +
 P.intermedia, T.forsythia + IL6 + IL13 + F.nucleatum, Calprotectin + T.denticola + IL10 +
 F.nucleatum, MMP9 + P.gingivalis + IL13 + C.rectus, T.forsythia + IL10 + IL2 +
 P.intermedia, MMP8 + OPG + P.gingivalis + C.rectus, Calprotectin + T.forsythia + IL2 +
 C.rectus, MMP9 + P.gingivalis + IL10 + C.rectus, T.forsythia + ICTP + IL13 + F.nucleatum,
 MMP8 + OPG + P.gingivalis + F.nucleatum, MMP8 + P.gingivalis + IL6 + F.nucleatum,
 Calprotectin + T.denticola + IL13 + F.nucleatum, MMP9 + OPG + T.forsythia +
 F.nucleatum, MMP9 + P.gingivalis + IL2 + C.rectus, P.gingivalis + T.denticola + IL13 + IL4,
 Calprotectin + P.gingivalis + T.denticola + IL10, Calprotectin + T.forsythia + IL4 + C.rectus,
 OPG + T.forsythia + IL10 + P.intermedia, P.gingivalis + IL6 + IL10 + P.intermedia,
 P.gingivalis + IL6 + IL2 + P.intermedia, MMP8 + T.forsythia + IL2 + F.nucleatum,
 Calprotectin + T.denticola + TNFa + F.nucleatum, MMP9 + T.forsythia + IL10 +
 F.nucleatum, OPG + P.gingivalis + IL6 + P.intermedia, OPG + T.forsythia + IL4 +
 P.intermedia, P.gingivalis + T.denticola + IL13 + TNFa, T.forsythia + IL1beta + IL2 +
 P.intermedia, T.forsythia + IL1beta + IL4 + P.intermedia, MMP8 + MMP9 + T.forsythia +
 F.nucleatum, MMP8 + P.gingivalis + TNFa + C.rectus, P.gingivalis + IL6 + ICTP + C.rectus,
 Calprotectin + P.gingivalis + T.denticola + IL2, Calprotectin + P.gingivalis + IL6 +
 F.nucleatum, P.gingivalis + IL1beta + IL10 + P.intermedia, T.forsythia + ICTP + IL13 +
 C.rectus, MMP8 + P.gingivalis + IL4 + C.rectus, P.gingivalis + T.forsythia + IL6 + TNFa,
 P.gingivalis + T.forsythia + ICTP + IL13, T.forsythia + IL6 + IL4 + P.intermedia, MMP8 +
 P.gingivalis + IL1beta + C.rectus, MMP8 + T.forsythia + IL10 + F.nucleatum, MMP9 +

P.gingivalis + IL1beta + C.rectus, P.gingivalis + IL13 + TNFa + P.intermedia, MMP9 +
 P.gingivalis + IL4 + F.nucleatum, T.denticola + IL6 + IL13 + F.nucleatum, OPG +
 P.gingivalis + TNFa + P.intermedia, T.forsythia + ICTP + TNFa + F.nucleatum, MMP8 +
 P.gingivalis + IL10 + C.rectus, Calprotectin + T.denticola + IL4 + F.nucleatum, OPG +
 T.denticola + IL13 + F.nucleatum, P.gingivalis + IL1beta + TNFa + P.intermedia, T.forsythia
 + IL6 + IL2 + P.intermedia, T.denticola + IL10 + IL13 + F.nucleatum, T.denticola + IL2 +
 TNFa + F.nucleatum, MMP8 + MMP9 + P.gingivalis + F.nucleatum, Calprotectin +
 P.gingivalis + ICTP + C.rectus, OPG + T.denticola + IL6 + F.nucleatum, MMP8 +
 P.gingivalis + TNFa + F.nucleatum, OPG + P.gingivalis + IL1beta + P.intermedia, OPG +
 P.gingivalis + IL4 + P.intermedia, P.gingivalis + T.forsythia + IL10 + IL13, P.gingivalis +
 IL1beta + IL2 + P.intermedia, P.gingivalis + IL1beta + IL4 + P.intermedia, T.forsythia + IL6
 + ICTP + F.nucleatum, MMP8 + P.gingivalis + IL13 + C.rectus, Calprotectin + T.denticola +
 IL1beta + F.nucleatum, MMP9 + P.gingivalis + IL13 + F.nucleatum, P.gingivalis +
 T.forsythia + IL6 + IL4, P.gingivalis + IL10 + TNFa + P.intermedia, Calprotectin +
 P.gingivalis + T.forsythia + IL10, Calprotectin + P.gingivalis + IL10 + C.rectus, P.gingivalis
 + T.forsythia + ICTP + IL10, P.gingivalis + IL4 + TNFa + P.intermedia, OPG + P.gingivalis
 + IL10 + P.intermedia, OPG + P.gingivalis + IL2 + P.intermedia, MMP8 + P.gingivalis + IL6
 + C.rectus, MMP8 + P.gingivalis + IL4 + F.nucleatum, Calprotectin + P.gingivalis +
 T.denticola + IL1beta, Calprotectin + T.forsythia + IL2 + F.nucleatum, OPG + P.gingivalis +
 T.forsythia + ICTP, P.gingivalis + T.denticola + IL6 + IL1beta, P.gingivalis + T.denticola +
 IL6 + IL2, P.gingivalis + IL2 + IL4 + P.intermedia, P.gingivalis + IL2 + TNFa +
 P.intermedia, MMP8 + P.gingivalis + IL2 + F.nucleatum, OPG + T.denticola + IL10 +
 F.nucleatum, P.gingivalis + IL10 + IL2 + P.intermedia, T.denticola + IL2 + IL13 +
 F.nucleatum, Calprotectin + P.gingivalis + T.denticola + TNFa, MMP9 + P.gingivalis + IL2
 + F.nucleatum, P.gingivalis + T.forsythia + IL6 + IL1beta, P.gingivalis + T.denticola + IL10
 + IL2, MMP8 + P.gingivalis + IL13 + F.nucleatum, OPG + T.denticola + IL2 + F.nucleatum,
 P.gingivalis + T.denticola + IL6 + IL10, P.gingivalis + T.denticola + IL6 + TNFa, MMP9 +
 OPG + P.gingivalis + F.nucleatum, T.forsythia + IL2 + IL4 + P.intermedia, OPG +
 T.denticola + TNFa + F.nucleatum, P.gingivalis + T.denticola + IL6 + IL4, P.gingivalis +
 T.denticola + IL2 + TNFa, T.forsythia + IL10 + IL13 + F.nucleatum, Calprotectin +
 T.forsythia + IL10 + F.nucleatum, P.gingivalis + T.forsythia + IL6 + IL10, Calprotectin +
 P.gingivalis + T.denticola + IL4, Calprotectin + P.gingivalis + IL10 + F.nucleatum, OPG +
 T.denticola + IL1beta + F.nucleatum, P.gingivalis + IL10 + IL4 + P.intermedia, T.forsythia +
 ICTP + IL10 + C.rectus, P.gingivalis + T.denticola + IL10 + TNFa, P.gingivalis + T.forsythia
 + IL6 + IL2, P.gingivalis + T.denticola + IL1beta + IL10, P.gingivalis + T.denticola +

IL1beta + IL2, T.forsythia + IL6 + TNFa + C.rectus, Calprotectin + P.gingivalis + T.forsythia + IL4, OPG + T.forsythia + IL13 + F.nucleatum, MMP8 + P.gingivalis + IL2 + C.rectus, Calprotectin + P.gingivalis + T.forsythia + TNFa, OPG + P.gingivalis + T.forsythia + IL10, T.forsythia + IL6 + TNFa + F.nucleatum, T.denticola + IL6 + IL10 + F.nucleatum, Calprotectin + P.gingivalis + T.forsythia + IL2, OPG + T.forsythia + ICTP + F.nucleatum, OPG + T.forsythia + ICTP + C.rectus, P.gingivalis + T.denticola + IL10 + IL4, T.denticola + IL6 + IL1beta + F.nucleatum, Calprotectin + P.gingivalis + IL4 + C.rectus, P.gingivalis + T.forsythia + ICTP + IL2, P.gingivalis + T.denticola + IL2 + IL4, T.forsythia + ICTP + IL2 + F.nucleatum, P.gingivalis + T.forsythia + ICTP + IL4, P.gingivalis + T.forsythia + IL1beta + IL13, Calprotectin + P.gingivalis + IL2 + C.rectus, P.gingivalis + T.forsythia + ICTP + TNFa, T.denticola + IL13 + IL4 + F.nucleatum, T.denticola + IL6 + TNFa + F.nucleatum, OPG + T.denticola + IL4 + F.nucleatum, Calprotectin + P.gingivalis + T.forsythia + IL1beta, T.forsythia + IL6 + IL1beta + F.nucleatum, T.forsythia + ICTP + IL4 + F.nucleatum, T.forsythia + IL2 + IL13 + F.nucleatum, T.denticola + IL1beta + IL10 + F.nucleatum, Calprotectin + P.gingivalis + TNFa + C.rectus, OPG + T.forsythia + TNFa + F.nucleatum, T.forsythia + ICTP + IL1beta + F.nucleatum, T.denticola + IL10 + TNFa + F.nucleatum, Calprotectin + P.gingivalis + IL1beta + C.rectus, OPG + P.gingivalis + T.forsythia + IL13, T.forsythia + ICTP + IL10 + F.nucleatum, T.forsythia + ICTP + TNFa + C.rectus, T.denticola + IL6 + IL2 + F.nucleatum, T.forsythia + IL1beta + IL13 + F.nucleatum, OPG + T.forsythia + IL6 + F.nucleatum, T.forsythia + IL10 + IL13 + C.rectus, T.forsythia + ICTP + IL4 + C.rectus, P.gingivalis + T.forsythia + IL2 + IL13, P.gingivalis + T.forsythia + IL13 + TNFa, T.forsythia + IL6 + IL4 + C.rectus, T.forsythia + ICTP + IL1beta + C.rectus, P.gingivalis + T.forsythia + ICTP + IL1beta, T.denticola + IL1beta + IL2 + F.nucleatum, T.denticola + IL1beta + IL13 + F.nucleatum, P.gingivalis + T.denticola + IL4 + TNFa, T.forsythia + IL13 + IL4 + F.nucleatum, T.denticola + IL6 + IL4 + F.nucleatum, T.forsythia + IL6 + IL1beta + C.rectus, T.forsythia + IL6 + IL10 + C.rectus, OPG + P.gingivalis + T.forsythia + IL2, T.forsythia + IL6 + IL2 + C.rectus, P.gingivalis + T.denticola + IL1beta + IL4, T.forsythia + ICTP + IL2 + C.rectus, Calprotectin + P.gingivalis + IL13 + F.nucleatum, P.gingivalis + IL6 + TNFa + F.nucleatum, T.forsythia + IL6 + IL4 + F.nucleatum, T.denticola + IL2 + IL4 + F.nucleatum, OPG + P.gingivalis + T.forsythia + IL4, OPG + T.forsythia + IL6 + C.rectus, P.gingivalis + IL6 + IL13 + F.nucleatum, Calprotectin + P.gingivalis + TNFa + F.nucleatum, P.gingivalis + IL10 + IL13 + F.nucleatum, OPG + P.gingivalis + T.forsythia + TNFa, P.gingivalis + T.forsythia + IL13 + IL4, P.gingivalis + ICTP + IL10 + F.nucleatum, Calprotectin + P.gingivalis + IL2 + F.nucleatum, Calprotectin + P.gingivalis + IL4 + F.nucleatum, T.forsythia + IL13 + TNFa + F.nucleatum, T.denticola +

IL13 + TNFa + F.nucleatum, Calprotectin + P.gingivalis + IL13 + C.rectus, T.denticola + IL10 + IL4 + F.nucleatum, P.gingivalis + T.denticola + IL1beta + TNFa, OPG + T.forsythia + IL4 + C.rectus, OPG + T.forsythia + IL1beta + C.rectus, OPG + T.forsythia + IL13 + C.rectus, P.gingivalis + T.forsythia + IL10 + IL2, T.forsythia + IL10 + TNFa + F.nucleatum, Calprotectin + P.gingivalis + IL1beta + F.nucleatum, OPG + T.forsythia + IL4 + F.nucleatum, P.gingivalis + ICTP + IL1beta + F.nucleatum, T.forsythia + IL1beta + TNFa + F.nucleatum, OPG + P.gingivalis + IL6 + F.nucleatum, OPG + T.forsythia + IL1beta + F.nucleatum, T.forsythia + IL4 + TNFa + F.nucleatum, OPG + P.gingivalis + T.forsythia + IL1beta, T.denticola + IL1beta + IL4 + F.nucleatum, OPG + T.forsythia + TNFa + C.rectus, P.gingivalis + IL6 + IL1beta + F.nucleatum, P.gingivalis + IL6 + IL13 + C.rectus, T.forsythia + IL6 + IL10 + F.nucleatum, T.forsythia + IL6 + IL2 + F.nucleatum, T.forsythia + IL13 + TNFa + C.rectus, OPG + T.forsythia + IL2 + F.nucleatum, OPG + T.forsythia + IL2 + C.rectus, P.gingivalis + IL6 + IL10 + F.nucleatum, T.forsythia + IL13 + IL4 + C.rectus, OPG + P.gingivalis + ICTP + F.nucleatum, T.forsythia + IL2 + IL13 + C.rectus, T.forsythia + IL2 + TNFa + F.nucleatum, T.denticola + IL10 + IL2 + F.nucleatum, T.denticola + IL4 + TNFa + F.nucleatum, P.gingivalis + T.forsythia + IL10 + IL4, OPG + T.forsythia + IL10 + F.nucleatum, P.gingivalis + IL6 + IL4 + F.nucleatum, T.forsythia + IL1beta + IL13 + C.rectus, P.gingivalis + IL6 + IL2 + F.nucleatum, P.gingivalis + ICTP + IL4 + F.nucleatum, P.gingivalis + ICTP + IL2 + F.nucleatum, OPG + T.forsythia + IL10 + C.rectus, P.gingivalis + T.forsythia + IL2 + IL4, T.forsythia + IL1beta + IL10 + F.nucleatum, T.forsythia + IL1beta + IL2 + F.nucleatum, OPG + P.gingivalis + IL6 + C.rectus, P.gingivalis + T.forsythia + IL1beta + IL10, T.forsythia + IL1beta + IL4 + F.nucleatum, T.forsythia + IL2 + IL4 + F.nucleatum, P.gingivalis + T.forsythia + IL10 + TNFa, T.forsythia + IL2 + IL4 + C.rectus, T.denticola + IL1beta + TNFa + F.nucleatum, T.forsythia + IL1beta + IL4 + C.rectus, T.forsythia + IL2 + TNFa + C.rectus, T.forsythia + IL1beta + IL10 + C.rectus, T.forsythia + IL1beta + IL2 + C.rectus, T.forsythia + IL1beta + TNFa + C.rectus, T.forsythia + IL10 + IL4 + F.nucleatum, P.gingivalis + T.forsythia + IL2 + TNFa, P.gingivalis + IL6 + TNFa + C.rectus, P.gingivalis + IL6 + IL4 + C.rectus, P.gingivalis + ICTP + TNFa + F.nucleatum, MMP8 + Calprotectin + P.intermedia + C.rectus, P.gingivalis + IL6 + IL2 + C.rectus, P.gingivalis + IL6 + IL1beta + C.rectus, OPG + P.gingivalis + IL10 + F.nucleatum, P.gingivalis + ICTP + IL13 + F.nucleatum, T.forsythia + IL10 + IL4 + C.rectus, T.forsythia + IL10 + TNFa + C.rectus, T.forsythia + IL4 + TNFa + C.rectus, P.gingivalis + ICTP + IL10 + C.rectus, P.gingivalis + ICTP + IL1beta + C.rectus, P.gingivalis + ICTP + IL4 + C.rectus, P.gingivalis + T.forsythia + IL1beta + IL4, P.gingivalis + ICTP + IL2 + C.rectus, P.gingivalis + T.forsythia + IL4 + TNFa, P.gingivalis + ICTP + TNFa + C.rectus, T.forsythia + IL10 +

IL2 + F.nucleatum, Calprotectin + MMP9 + P.intermedia + C.rectus, P.gingivalis + IL6 + IL10 + C.rectus, OPG + P.gingivalis + ICTP + C.rectus, P.gingivalis + T.forsythia + IL1beta + TNFa, Calprotectin + MMP9 + P.intermedia + F.nucleatum, P.gingivalis + T.forsythia + IL1beta + IL2, MMP8 + Calprotectin + P.intermedia + F.nucleatum, T.forsythia + IL10 + IL2 + C.rectus, P.gingivalis + ICTP + IL13 + C.rectus, P.gingivalis + IL10 + TNFa + F.nucleatum, MMP8 + ICTP + P.intermedia + F.nucleatum, MMP8 + ICTP + P.intermedia + C.rectus, OPG + P.gingivalis + IL4 + F.nucleatum, P.gingivalis + IL10 + IL2 + F.nucleatum, P.gingivalis + IL1beta + IL10 + F.nucleatum, P.gingivalis + IL10 + IL4 + F.nucleatum, OPG + P.gingivalis + IL1beta + F.nucleatum, MMP8 + TNFa + P.intermedia + F.nucleatum, OPG + P.gingivalis + IL2 + F.nucleatum, P.gingivalis + IL13 + IL4 + F.nucleatum, OPG + P.gingivalis + TNFa + F.nucleatum, P.gingivalis + IL1beta + IL4 + F.nucleatum, P.gingivalis + IL2 + IL13 + F.nucleatum, P.gingivalis + IL2 + IL4 + F.nucleatum, OPG + P.gingivalis + IL13 + F.nucleatum, P.gingivalis + IL2 + TNFa + F.nucleatum, P.gingivalis + IL1beta + IL2 + F.nucleatum, P.gingivalis + IL4 + TNFa + F.nucleatum, P.gingivalis + IL13 + TNFa + F.nucleatum, P.gingivalis + IL1beta + IL13 + F.nucleatum, P.gingivalis + IL1beta + TNFa + F.nucleatum, MMP8 + IL1beta + P.intermedia + F.nucleatum, MMP8 + TNFa + P.intermedia + C.rectus, P.gingivalis + IL10 + IL13 + C.rectus, MMP9 + TNFa + P.intermedia + C.rectus, P.gingivalis + IL1beta + IL10 + C.rectus, OPG + P.gingivalis + IL10 + C.rectus, MMP8 + IL1beta + P.intermedia + C.rectus, P.gingivalis + IL1beta + IL2 + C.rectus, P.gingivalis + IL10 + IL2 + C.rectus, P.gingivalis + IL2 + IL13 + C.rectus, Calprotectin + TNFa + P.intermedia + F.nucleatum, MMP9 + TNFa + P.intermedia + F.nucleatum, OPG + P.gingivalis + IL13 + C.rectus, MMP8 + IL10 + P.intermedia + F.nucleatum, MMP8 + IL6 + P.intermedia + F.nucleatum, OPG + P.gingivalis + IL1beta + C.rectus, P.gingivalis + IL13 + IL4 + C.rectus, Calprotectin + ICTP + P.intermedia + F.nucleatum, MMP9 + IL1beta + P.intermedia + C.rectus, MMP9 + ICTP + P.intermedia + C.rectus, OPG + P.gingivalis + IL2 + C.rectus, OPG + P.gingivalis + TNFa + C.rectus, MMP8 + OPG + P.intermedia + F.nucleatum, OPG + P.gingivalis + IL4 + C.rectus, MMP8 + IL13 + P.intermedia + C.rectus, MMP8 + IL13 + P.intermedia + F.nucleatum, MMP9 + ICTP + P.intermedia + F.nucleatum, P.gingivalis + IL2 + IL4 + C.rectus, P.gingivalis + IL10 + TNFa + C.rectus, Calprotectin + ICTP + P.intermedia + C.rectus, MMP8 + IL2 + P.intermedia + F.nucleatum, P.gingivalis + IL10 + IL4 + C.rectus, MMP8 + MMP9 + P.intermedia + C.rectus, MMP8 + IL4 + P.intermedia + F.nucleatum, MMP9 + IL1beta + P.intermedia + F.nucleatum, P.gingivalis + IL13 + TNFa + C.rectus, MMP8 + MMP9 + P.intermedia + F.nucleatum, MMP8 + OPG + P.intermedia + C.rectus, MMP8 + IL10 + P.intermedia + C.rectus, MMP9 + IL2 + P.intermedia + C.rectus, P.gingivalis + IL2 + TNFa + C.rectus, Calprotectin + MMP9 +

F.nucleatum + C.rectus, MMP8 + IL2 + P.intermedia + C.rectus, MMP8 + IL6 +
 P.intermedia + C.rectus, P.gingivalis + IL1beta + IL4 + C.rectus, MMP9 + IL4 +
 P.intermedia + F.nucleatum, P.gingivalis + IL1beta + TNFa + C.rectus, P.gingivalis + IL4 +
 TNFa + C.rectus, MMP8 + IL4 + P.intermedia + C.rectus, Calprotectin + IL2 + P.intermedia
 + F.nucleatum, Calprotectin + IL10 + P.intermedia + F.nucleatum, Calprotectin + OPG +
 P.intermedia + F.nucleatum, Calprotectin + TNFa + P.intermedia + C.rectus, Calprotectin +
 IL13 + P.intermedia + F.nucleatum, MMP9 + IL2 + P.intermedia + F.nucleatum, P.gingivalis
 + IL1beta + IL13 + C.rectus, Calprotectin + IL6 + P.intermedia + F.nucleatum, MMP9 + IL6
 + P.intermedia + F.nucleatum, Calprotectin + IL1beta + P.intermedia + F.nucleatum,
 Calprotectin + IL4 + P.intermedia + F.nucleatum, MMP9 + IL6 + P.intermedia + C.rectus,
 Calprotectin + OPG + P.intermedia + C.rectus, MMP9 + IL13 + P.intermedia + C.rectus,
 MMP9 + OPG + P.intermedia + C.rectus, MMP9 + IL10 + P.intermedia + C.rectus,
 Calprotectin + IL10 + P.intermedia + C.rectus, Calprotectin + IL2 + P.intermedia + C.rectus,
 MMP9 + IL13 + P.intermedia + F.nucleatum, Calprotectin + IL6 + P.intermedia + C.rectus,
 Calprotectin + IL4 + P.intermedia + C.rectus, MMP9 + OPG + P.intermedia + F.nucleatum,
 IL4 + TNFa + P.intermedia + F.nucleatum, MMP8 + Calprotectin + F.nucleatum + C.rectus,
 MMP9 + IL10 + P.intermedia + F.nucleatum, Calprotectin + IL1beta + P.intermedia +
 C.rectus, Calprotectin + IL13 + P.intermedia + C.rectus, MMP9 + IL4 + P.intermedia +
 C.rectus, ICTP + TNFa + P.intermedia + F.nucleatum, IL1beta + TNFa + P.intermedia +
 F.nucleatum, IL10 + TNFa + P.intermedia + F.nucleatum, MMP8 + ICTP + F.nucleatum +
 C.rectus, ICTP + IL4 + P.intermedia + F.nucleatum, IL6 + ICTP + P.intermedia +
 F.nucleatum, ICTP + IL1beta + P.intermedia + F.nucleatum, MMP9 + ICTP + F.nucleatum +
 C.rectus, ICTP + IL2 + P.intermedia + F.nucleatum, IL2 + TNFa + P.intermedia +
 F.nucleatum, ICTP + TNFa + P.intermedia + C.rectus, ICTP + IL10 + P.intermedia +
 F.nucleatum, IL13 + TNFa + P.intermedia + F.nucleatum, ICTP + IL13 + P.intermedia +
 F.nucleatum, OPG + ICTP + P.intermedia + F.nucleatum, IL6 + TNFa + P.intermedia +
 F.nucleatum, OPG + TNFa + P.intermedia + F.nucleatum, Calprotectin + IL10 + F.nucleatum
 + C.rectus, IL6 + ICTP + P.intermedia + C.rectus, Calprotectin + OPG + F.nucleatum +
 C.rectus, IL13 + IL4 + P.intermedia + F.nucleatum, MMP9 + TNFa + F.nucleatum +
 C.rectus, IL4 + TNFa + P.intermedia + C.rectus, OPG + IL4 + P.intermedia + F.nucleatum,
 OPG + ICTP + P.intermedia + C.rectus, ICTP + IL4 + P.intermedia + C.rectus, ICTP + IL10
 + P.intermedia + C.rectus, IL2 + IL4 + P.intermedia + F.nucleatum, ICTP + IL1beta +
 P.intermedia + C.rectus, MMP9 + IL6 + F.nucleatum + C.rectus, IL10 + IL2 + P.intermedia +
 F.nucleatum, IL6 + IL10 + P.intermedia + F.nucleatum, IL6 + IL4 + P.intermedia +
 F.nucleatum, IL1beta + IL4 + P.intermedia + F.nucleatum, Calprotectin + IL1beta +

F.nucleatum + C.rectus, ICTP + IL2 + P.intermedia + C.rectus, IL10 + IL4 + P.intermedia +
 F.nucleatum, ICTP + IL13 + P.intermedia + C.rectus, OPG + IL2 + P.intermedia +
 F.nucleatum, IL1beta + IL10 + P.intermedia + F.nucleatum, MMP8 + TNFa + F.nucleatum +
 C.rectus, MMP9 + OPG + F.nucleatum + C.rectus, OPG + IL10 + P.intermedia +
 F.nucleatum, IL1beta + IL13 + P.intermedia + F.nucleatum, IL2 + IL13 + P.intermedia +
 F.nucleatum, MMP9 + IL2 + F.nucleatum + C.rectus, MMP9 + IL13 + F.nucleatum +
 C.rectus, OPG + IL1beta + P.intermedia + F.nucleatum, IL6 + IL1beta + P.intermedia +
 F.nucleatum, IL1beta + IL2 + P.intermedia + F.nucleatum, Calprotectin + IL6 + F.nucleatum
 + C.rectus, IL10 + IL13 + P.intermedia + F.nucleatum, OPG + IL6 + P.intermedia +
 F.nucleatum, IL6 + IL2 + P.intermedia + F.nucleatum, IL10 + TNFa + P.intermedia +
 C.rectus, Calprotectin + ICTP + F.nucleatum + C.rectus, MMP8 + MMP9 + F.nucleatum +
 C.rectus, MMP9 + IL1beta + F.nucleatum + C.rectus, MMP8 + IL10 + F.nucleatum +
 C.rectus, Calprotectin + IL4 + F.nucleatum + C.rectus, MMP9 + IL10 + F.nucleatum +
 C.rectus, OPG + IL13 + P.intermedia + F.nucleatum, IL6 + IL13 + P.intermedia +
 F.nucleatum, IL1beta + TNFa + P.intermedia + C.rectus, MMP9 + IL4 + F.nucleatum +
 C.rectus, IL6 + TNFa + P.intermedia + C.rectus, IL2 + TNFa + P.intermedia + C.rectus,
 Calprotectin + IL13 + F.nucleatum + C.rectus, MMP8 + IL6 + F.nucleatum + C.rectus,
 MMP8 + IL13 + F.nucleatum + C.rectus, MMP8 + IL4 + F.nucleatum + C.rectus, MMP8 +
 IL1beta + F.nucleatum + C.rectus, IL13 + IL4 + P.intermedia + C.rectus, IL6 + IL4 +
 P.intermedia + C.rectus, MMP8 + OPG + F.nucleatum + C.rectus, IL13 + TNFa +
 P.intermedia + C.rectus, OPG + TNFa + P.intermedia + C.rectus, Calprotectin + TNFa +
 F.nucleatum + C.rectus, MMP8 + IL2 + F.nucleatum + C.rectus, IL6 + IL1beta +
 P.intermedia + C.rectus, IL10 + IL4 + P.intermedia + C.rectus, IL2 + IL4 + P.intermedia +
 C.rectus, IL6 + IL13 + P.intermedia + C.rectus, IL1beta + IL4 + P.intermedia + C.rectus,
 OPG + IL4 + P.intermedia + C.rectus, Calprotectin + IL2 + F.nucleatum + C.rectus, IL10 +
 IL13 + P.intermedia + C.rectus, IL6 + IL2 + P.intermedia + C.rectus, IL10 + IL2 +
 P.intermedia + C.rectus, IL6 + IL10 + P.intermedia + C.rectus, IL2 + IL13 + P.intermedia +
 C.rectus, OPG + IL2 + P.intermedia + C.rectus, OPG + IL1beta + P.intermedia + C.rectus,
 OPG + IL10 + P.intermedia + C.rectus, OPG + IL13 + P.intermedia + C.rectus, IL1beta +
 IL10 + P.intermedia + C.rectus, IL1beta + IL13 + P.intermedia + C.rectus, IL1beta + IL2 +
 P.intermedia + C.rectus, OPG + IL6 + P.intermedia + C.rectus, IL6 + ICTP + F.nucleatum +
 C.rectus, IL4 + TNFa + F.nucleatum + C.rectus, ICTP + IL1beta + F.nucleatum + C.rectus,
 ICTP + IL4 + F.nucleatum + C.rectus, ICTP + TNFa + F.nucleatum + C.rectus, ICTP + IL10
 + F.nucleatum + C.rectus, IL6 + IL4 + F.nucleatum + C.rectus, IL6 + TNFa + F.nucleatum +
 C.rectus, ICTP + IL13 + F.nucleatum + C.rectus, OPG + ICTP + F.nucleatum + C.rectus,

ICTP + IL2 + F.nucleatum + C.rectus, OPG + IL6 + F.nucleatum + C.rectus, IL6 + IL1beta + F.nucleatum + C.rectus, IL6 + IL2 + F.nucleatum + C.rectus, IL6 + IL10 + F.nucleatum + C.rectus, IL6 + IL13 + F.nucleatum + C.rectus, IL2 + IL4 + F.nucleatum + C.rectus, IL10 + TNFa + F.nucleatum + C.rectus, IL13 + IL4 + F.nucleatum + C.rectus, OPG + IL4 + F.nucleatum + C.rectus, IL1beta + IL10 + F.nucleatum + C.rectus, OPG + IL1beta + F.nucleatum + C.rectus, IL1beta + IL4 + F.nucleatum + C.rectus, IL10 + IL13 + F.nucleatum + C.rectus, OPG + IL10 + F.nucleatum + C.rectus, IL1beta + IL13 + F.nucleatum + C.rectus, IL13 + TNFa + F.nucleatum + C.rectus, IL10 + IL4 + F.nucleatum + C.rectus, OPG + IL13 + F.nucleatum + C.rectus, IL1beta + IL2 + F.nucleatum + C.rectus, IL10 + IL2 + F.nucleatum + C.rectus, IL1beta + TNFa + F.nucleatum + C.rectus, IL2 + IL13 + F.nucleatum + C.rectus, OPG + TNFa + F.nucleatum + C.rectus, IL2 + TNFa + F.nucleatum + C.rectus, and OPG + IL2 + F.nucleatum + C.rectus.

[0026] The present invention provides a method wherein the probability of oral disease is calculated comprising the steps of: determining the levels of two or more biomarkers in said first individual and a second individual, generating a receiver operating characteristic (ROC) curve, and calculating area under said ROC curve (AUC), said area providing the probability of said oral disease.

[0027] In various aspects of the invention, the sample is selected from the group consisting of a bodily fluid, tissue and organ.

[0028] In some aspects, the fluid is saliva.

[0029] In other aspects of the invention, the biomarker levels are biomarker protein levels in the sample.

[0030] In an embodiment of the invention, the oral disease is periodontal disease.

[0031] In another embodiment, the oral disease is peri-implant disease.

[0032] The present invention also provides a kit for carrying out different embodiments of the method of the invention, the kit comprising: a) a sterile container for sample collection, and b) one or more components selected from the group consisting of one or more reagents for performing the assay, a calibration standard and a quality control sample.

DESCRIPTION OF THE DRAWINGS

[0033] Figure 1 depicts a receiver operating characteristic curve (ROC) and area under the curve data for the combination of MMP-8 and MMP-9.

[0034] Figure 2 depicts a receiver operating characteristic curve (ROC) and area under the curve data for the combination of MMP-8 and ICTP.

[0035] Figure 3 depicts a receiver operating characteristic curve (ROC) and area under the curve data for the combination of MMP-8, MMP-9 and IL-1 β .

[0036] Figure 4 depicts a receiver operating characteristic curve (ROC) and area under the curve data for the combination of MMP-8, MMP-9 and ICTP.

[0037] Figure 5 depicts a receiver operating characteristic curve (ROC) and area under the curve data for the combination of MMP-8, MMP-9, IL-1 β and ICTP.

[0038] Figure 6 depicts a receiver operating characteristic curve (ROC) and area under the curve data for the combination of MMP-8, MMP-9, IL-1 β , ICTP and Calprotectin.

[0039] Figure 7 depicts a classification and regression tree analysis (CART) showing multiple combinations of biomarkers that can discriminate among various disease states.

[0040] Figure 8 depicts the stratification of the low-risk population and the disease-susceptible population into four groups following the criteria of clinical attachment loss, periodontal probing depth, radiographic bone loss, and bleeding on probing (BOP).

[0041] Figure 9 depicts ROCs of combinatorial permutations of salivary biomarkers coupled with biofilm subgingival pathogens measured by quantitative PCT (qPCR). AUC = area under the curve; OR= odds ratio, numbers in brackets are 95% confidence intervals.

DETAILED DESCRIPTION OF THE INVENTION

[0042] Demonstrated herein is a method using combinations of 14 pro-inflammatory and bone-specific markers from patient samples coupled with plaque biofilm pathogens (collectively referred to herein as "biomarkers" and used interchangeably) for the identification of periodontal disease. This novel combinatorial approach resulted in robust probability predictions of periodontitis in human subjects.

[0043] As used herein, "probability" is a calculated numerical likelihood based on an AUC value derived from a ROC curve and not simply a vague likelihood of a disease state.

[0044] As used herein, "oral disease" includes periodontal disease, peri-implant disease or any other gingival disease.

[0045] As used herein, the term "biomarker" means a substance that is measured objectively and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

[0046] Provided herein is a method to accurately identify clinical signs of periodontal disease by a multi-analyte measurement of salivary biomarkers indicative of periodontitis. The described approach evaluates multiple analytes in oral fluids that, when combined, identify and permit calculation of a probability of the patient disease state. Supporting data demonstrate that the biomarkers, for example, matrix metalloproteinase-8 (MMP-8), matrix metalloproteinase-9 (MMP-9), pyridinoline-cross-linked carboxyterminal telopeptide of type I collagen (ICTP), interleukin-1 beta (IL-1) and calprotectin as well as other biomarkers described herein used in various permutations result in a high level of prediction of periodontal disease status is achieved. Various combinations of the foregoing biomarkers were analyzed using a "receiver operating characteristics curve" (herein after "ROC"). A ROC curve is a graphical plot of the sensitivity versus (1 - specificity) for a binary classifier or diagnostic system as its discrimination threshold is varied. The model maps outcomes into classes or groups. The classifier or "diagnosis" may be a continuous output of values in which the boundary between classes is determined by a threshold value, or it may be a discrete label indicating one of a limited number of outcomes (typically two, *e.g.*, positive or negative). For a binary (two-class) predictive problem in which the classes are identified as either positive (p) or negative (n) there are four possible outcomes. If the outcome from a prediction is p and the actual value is also p, then it is called a true positive (TP); however if the actual value is n then it is said a false positive (FP). Conversely, a true negative has occurred when both the prediction outcome and the actual value are n, and false negative is when the prediction outcome is n while the actual value is p. The ROC curve displays the outcomes graphically by plotting the fraction of true positive results versus the fraction of false positive results and the area under the curve (AUC) of this plot provides a relative measure of the accuracy of the diagnosis, or the probability of oral disease. In particular, the closer the ROC curve follows the left-hand border and then the top border of the plot, the more accurate the diagnosis, while conversely the closer the curve comes to the 45-degree diagonal between the plot axes, the less accurate the diagnosis.

[0047] In general, ROC curves and AUC values are generated as follows. For a given sample of subjects, some of whom are healthy and some of whom are diseased, we have measured the value of a biomarker "Y" for each of the subjects, and we assume that higher values of "Y" are more indicative of disease. Next, a value "c" is chosen. For this value of "c", a pair of values (FPF, TPF) are computed, in which

[0048] (1) FPF = false positive fraction
 = percentage of healthy subjects with a "Y" value above "c"

[0049] (2) TPF = true positive fraction

= percentage of diseased subjects with a "Y" value above "c"

[0050] (FPF, TPF) is then generated for a continuum of values of "c" and then a scatterplot of these pairs is produced, with FPF on the x-axis and TPF on the y-axis. The curve that connects the points in this scatterplot is known as a receiver operating characteristic (ROC) curve.

[0051] The area under the ROC curve is referred to as the AUC and can be computed using the standard trapezoidal rule. It is also well-established that the value of AUC derived from the trapezoidal rule is equivalent to the Mann-Whitney U-statistic used to compare the median values of "Y" between healthy and diseased subjects. AUC values range from 0.5, which indicates that "Y" is useless for predicting disease, and 1.0, which indicates that "Y" is perfect for predicting disease.

[0052] The biomarkers discussed hereinabove individually demonstrate a high AUC and were used in determining the probability of periodontitis, if measured solely by AUC. In addition, the utilization of a classification and regression tree analysis (CART) shown in Figure 7 determined multiple combinations of biomarkers that can best discriminate among various disease states. This method allows highly accurate measures of disease status leading to accurate diagnostic indices (high sensitivity, specificity) (>0.9) and strong and significant odds ratios for disease classification prediction (OR > 20). Further, disclosure is included regarding a lab-on-a-chip demonstration of a diagnostic developed for one of these putative biomarkers (MMP-8) in saliva.

[0053] As recently reviewed, these biomarkers represent three distinct phases of periodontal disease – periodontal tissue inflammation, matrix degradation and alveolar bone resorption (Kinney *et al.*, 2007, Ann N Y Acad Sci 1098: 230-251). The complementation of the dataset with subgingival biofilm proportions supplements the microbe-host influences on periodontal disease identification to accepted clinical measures of disease. These results describe the development of disease signatures for periodontitis using rapid diagnostic techniques.

[0054] During the initiation of an inflammatory response in the periodontal connective tissue, numerous cytokines such as PGE₂, IL-1 β , IL-6, or TNF- α are released from cells of the junctional epithelia, connective tissue fibroblasts, and macrophages. Additionally, a number of enzymes such as MMP-8, MMP-9, or calprotectin are produced by PMNs and osteoclasts, leading to the degradation of connective tissue collagen and alveolar bone.

During connective tissue inflammation and following bone resorption, cytokines and bone resorptive/turnover proteins migrate towards the gingival sulcus or periodontal pocket and further into GCF where they are released into and contribute to whole saliva. The host-cell-derived matrix metalloproteinases MMP-8 and MMP-9 are believed to mediate, to a substantial extent, the matrix-destroying events during the stages of periodontal disease.

[0055] Biostatistical methods for the quality assessment of biomarkers today consist of determining if one single biomarker has both adequate reliability (repeatability) and validity for its use in diagnostic applications (Looney, 2004, Statistical Methods for Assessing Biomarkers. In: Looney SW, editor. Biostatistical Methods. Louisville: Humana Press, Inc Baker & Taylor. pp. 81-106). With previous research on the detection of periodontal biomarkers in GCF, both reliability and validity have been well demonstrated for all the 14 biomarkers selected in this study. The individual correlation of each biomarker with disease via receiver operating characteristic (ROC) curves and nonparametric estimates of the area under the ROC curve (AUC) was assessed from subjects above the selected threshold of each biomarker.

[0056] Specific biofilm organisms or exposures may have the capacity to affect the "inflammatory set point" of the local tissues in certain patients via epigenetic mechanisms (Bobetsis *et al.*, 2007, J Dent Res 86: 169-174; Kornman *et al.*, 2002, Re: A critical assessment of interleukin-1 (IL-1) genotyping when used in a genetic susceptibility test for severe chronic periodontitis. Greenstein G, Hart TC (2002;73:231-247). J Periodontol 73: 1553-1556; author reply 1556-1558). Thus, the utilization of rapid POC diagnostics that identify disease in the concept of the host-microbe interaction is demonstrated herein to lead to more rationally-tailored therapeutic strategies. The highest diagnostic accuracy in disease identification was noted when MMP-8 or MMP-9 was coupled with "red complex" periodontal organisms *T. denticola*, *P. gingivalis* or *T. forsythia* (Socransky *et al.*, 1998, J Clin Periodontol 25: 134-144). The concept of MMP-8 as a diagnostic has been well described (Herr *et al.*, 2007, Proc Natl Acad Sci U S A 104: 5268-5273; Christodoulides *et al.*, 2007, Ann N Y Acad Sci 1098: 411-428; Golub *et al.*, 1997, Inflamm Res 46: 310-319; Kinane *et al.*, 2003, J Periodontal Res 38: 400-404; Prescher *et al.*, 2007, Ann N Y Acad Sci 1098: 493-495) and the linkage between red complex bacteria and collagen destruction, previously reported (Oringer *et al.*, 1998, Clin Oral Implants Res 9: 365-373; Palys *et al.*, 1998, J Clin Periodontol 25: 865-871). The red complex bacteria are known for their potent ability to display trypsin-like enzyme activity that are responsible for destroying collagen matrices (Loesche *et al.*, 1987, J Periodontol 58: 266-273). Thus, these data substantiate the

combinatorial utilization of MMP-destroying enzymes and corresponding initiating pathogens such as *T. denticola* for periodontal disease identification. The data presented herein now support how the coupling of this information may lead to more accurate periodontal diagnoses from a biologic standpoint.

[0057] The utility of the methods provided is also demonstrated by the use of the combinations of biomarker levels to generate an AUC probability value that can diagnose oral disease. This probability value is useful in the diagnosis, determination of the susceptibility to, determination of the progression of, and determination of the effectiveness of treatment for oral disease.

[0058] Biomarkers contemplated for use in the present invention include but are not limited to *Aggregatibacter actinomycetemcomitans*, *Campylobacter rectus*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, matrix metalloproteinase-8 (MMP-8), matrix metalloproteinase-9 (MMP-9), osteoprotegerin (OPG), type I collagen pyridinoline cross-linked telopeptide (ICTP), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), interleukin-4 (IL-4), interleukin-10 (IL-10), interleukin-2 (IL-2), interleukin-13 (IL-13), calprotectin, and tumor necrosis factor α (TNF α).

[0059] The biomarker levels generated by the methods of the present invention are contemplated for use in combination to calculate AUC probability values that are indicative of relative disease state. Combinations of biomarkers for use in the present invention include but are not limited to those set out in Tables 1, 2 and 3 below.

Table 1. Biomarker combinations resulting in an AUC (probability) value greater than at least 70%.

<u>Signature</u>	<u>AUC</u>
Calprotectin + OPG + P.intermedia	0.79
MMP9 + IL13 + P.intermedia	0.79
MMP9 + P.intermedia	0.79
ICTP + TNFa + P.intermedia + F.nucleatum	0.79
P.gingivalis + TNFa	0.79
Calprotectin + IL13 + P.intermedia	0.79
MMP9 + IL10 + P.intermedia	0.79
Calprotectin + IL2 + P.intermedia	0.79
MMP8 + Calprotectin + C.rectus	0.79
Calprotectin + IL6 + P.intermedia	0.79
Calprotectin + IL1beta + P.intermedia	0.79

<u>Signature</u>	<u>AUC</u>
MMP9 + IL4 + P.intermedia	0.79
Calprotectin + IL10 + P.intermedia	0.79
IL1beta + TNFa + P.intermedia + F.nucleatum	0.79
IL10 + TNFa + P.intermedia + F.nucleatum	0.79
P.gingivalis	0.78
Calprotectin + IL4 + P.intermedia	0.78
Calprotectin + P.intermedia	0.78
MMP8 + ICTP + F.nucleatum + C.rectus	0.78
ICTP + IL4 + P.intermedia + F.nucleatum	0.78
IL6 + ICTP + P.intermedia + F.nucleatum	0.78
ICTP + IL1beta + P.intermedia + F.nucleatum	0.78
MMP9 + ICTP + F.nucleatum + C.rectus	0.78
ICTP + IL2 + P.intermedia + F.nucleatum	0.78
IL2 + TNFa + P.intermedia + F.nucleatum	0.78
ICTP + TNFa + P.intermedia + C.rectus	0.78
ICTP + IL10 + P.intermedia + F.nucleatum	0.78
IL13 + TNFa + P.intermedia + F.nucleatum	0.78
MMP8 + ICTP + C.rectus	0.78
ICTP + IL13 + P.intermedia + F.nucleatum	0.78
MMP9 + ICTP + C.rectus	0.78
ICTP + P.intermedia + F.nucleatum	0.78
OPG + ICTP + P.intermedia + F.nucleatum	0.78
IL6 + TNFa + P.intermedia + F.nucleatum	0.78
TNFa + P.intermedia + F.nucleatum	0.78
OPG + TNFa + P.intermedia + F.nucleatum	0.77
Calprotectin + IL10 + F.nucleatum + C.rectus	0.77
IL6 + ICTP + P.intermedia + C.rectus	0.77
Calprotectin + OPG + F.nucleatum + C.rectus	0.77
ICTP + TNFa + P.intermedia	0.77
IL13 + IL4 + P.intermedia + F.nucleatum	0.77
MMP9 + TNFa + F.nucleatum + C.rectus	0.77
IL4 + TNFa + P.intermedia + C.rectus	0.77
MMP9 + TNFa + C.rectus	0.77
OPG + IL4 + P.intermedia + F.nucleatum	0.77
OPG + ICTP + P.intermedia + C.rectus	0.77
ICTP + IL4 + P.intermedia + C.rectus	0.77
Calprotectin + MMP9 + F.nucleatum	0.77
ICTP + IL10 + P.intermedia + C.rectus	0.77
IL2 + IL4 + P.intermedia + F.nucleatum	0.77
IL4 + P.intermedia + F.nucleatum	0.77
ICTP + IL1beta + P.intermedia + C.rectus	0.77
MMP9 + IL6 + F.nucleatum + C.rectus	0.77
IL10 + IL2 + P.intermedia + F.nucleatum	0.77
MMP9 + IL6 + C.rectus	0.77
IL6 + IL10 + P.intermedia + F.nucleatum	0.77

<u>Signature</u>	<u>AUC</u>
IL6 + IL4 + P.intermedia + F.nucleatum	0.77
IL1beta + IL4 + P.intermedia + F.nucleatum	0.77
Calprotectin + IL1beta + F.nucleatum + C.rectus	0.77
ICTP + IL2 + P.intermedia + C.rectus	0.77
IL10 + IL4 + P.intermedia + F.nucleatum	0.77
ICTP + P.intermedia + C.rectus	0.77
IL4 + TNFa + P.intermedia	0.77
ICTP + IL13 + P.intermedia + C.rectus	0.77
OPG + IL2 + P.intermedia + F.nucleatum	0.76
IL1beta + IL10 + P.intermedia + F.nucleatum	0.76
P.intermedia + F.nucleatum + C.rectus	0.76
MMP8 + TNFa + F.nucleatum + C.rectus	0.76
IL10 + P.intermedia + F.nucleatum	0.76
MMP9 + OPG + F.nucleatum + C.rectus	0.76
OPG + IL10 + P.intermedia + F.nucleatum	0.76
IL1beta + IL13 + P.intermedia + F.nucleatum	0.76
IL2 + IL13 + P.intermedia + F.nucleatum	0.76
MMP9 + IL2 + F.nucleatum + C.rectus	0.76
MMP9 + IL13 + F.nucleatum + C.rectus	0.76
OPG + IL1beta + P.intermedia + F.nucleatum	0.76
IL1beta + P.intermedia + F.nucleatum	0.76
IL6 + ICTP + P.intermedia	0.76
IL6 + IL1beta + P.intermedia + F.nucleatum	0.76
IL1beta + IL2 + P.intermedia + F.nucleatum	0.76
Calprotectin + IL6 + F.nucleatum + C.rectus	0.76
IL10 + IL13 + P.intermedia + F.nucleatum	0.76
IL6 + P.intermedia + F.nucleatum	0.76
MMP8 + MMP9 + C.rectus	0.76
ICTP + IL4 + P.intermedia	0.76
OPG + IL6 + P.intermedia + F.nucleatum	0.76
IL6 + IL2 + P.intermedia + F.nucleatum	0.76
IL10 + TNFa + P.intermedia + C.rectus	0.76
OPG + P.intermedia + F.nucleatum	0.76
IL2 + P.intermedia + F.nucleatum	0.76
ICTP + IL1beta + P.intermedia	0.76
Calprotectin + ICTP + F.nucleatum + C.rectus	0.76
MMP8 + TNFa + C.rectus	0.76
MMP8 + MMP9 + F.nucleatum + C.rectus	0.76
MMP9 + IL1beta + F.nucleatum + C.rectus	0.76
MMP8 + IL10 + F.nucleatum + C.rectus	0.76
Calprotectin + IL4 + F.nucleatum + C.rectus	0.76
IL13 + P.intermedia + F.nucleatum	0.76
MMP9 + OPG + C.rectus	0.76
MMP9 + IL1beta + C.rectus	0.76
IL1beta + TNFa + P.intermedia	0.76

<u>Signature</u>	<u>AUC</u>
MMP9 + IL10 + F.nucleatum + C.rectus	0.76
OPG + IL13 + P.intermedia + F.nucleatum	0.76
IL6 + IL13 + P.intermedia + F.nucleatum	0.76
IL1beta + TNFa + P.intermedia + C.rectus	0.76
MMP9 + IL10 + C.rectus	0.76
MMP9 + IL4 + F.nucleatum + C.rectus	0.76
P.intermedia + F.nucleatum	0.76
ICTP + IL13 + P.intermedia	0.76
IL6 + TNFa + P.intermedia + C.rectus	0.76
IL6 + TNFa + P.intermedia	0.76
IL2 + TNFa + P.intermedia + C.rectus	0.76
Calprotectin + IL13 + F.nucleatum + C.rectus	0.76
MMP8 + IL10 + C.rectus	0.76
IL2 + TNFa + P.intermedia	0.76
MMP8 + IL6 + F.nucleatum + C.rectus	0.76
MMP8 + IL13 + F.nucleatum + C.rectus	0.76
MMP9 + F.nucleatum + C.rectus	0.76
MMP9 + IL2 + C.rectus	0.76
ICTP + IL2 + P.intermedia	0.76
MMP9 + IL13 + C.rectus	0.76
MMP9 + IL4 + C.rectus	0.76
MMP8 + IL4 + F.nucleatum + C.rectus	0.76
ICTP + IL10 + P.intermedia	0.76
IL10 + TNFa + P.intermedia	0.76
Calprotectin + OPG + C.rectus	0.76
MMP8 + IL1beta + F.nucleatum + C.rectus	0.76
TNFa + P.intermedia + C.rectus	0.76
IL13 + IL4 + P.intermedia + C.rectus	0.76
ICTP + P.intermedia	0.76
IL6 + IL4 + P.intermedia + C.rectus	0.76
MMP8 + ICTP + F.nucleatum	0.75
OPG + ICTP + P.intermedia	0.75
MMP8 + IL6 + C.rectus	0.75
MMP8 + IL1beta + C.rectus	0.75
MMP8 + OPG + F.nucleatum + C.rectus	0.75
IL13 + TNFa + P.intermedia + C.rectus	0.75
OPG + TNFa + P.intermedia + C.rectus	0.75
Calprotectin + MMP9	0.75
MMP8 + Calprotectin + F.nucleatum	0.75
MMP9 + C.rectus	0.75
MMP8 + IL13 + C.rectus	0.75
MMP8 + F.nucleatum + C.rectus	0.75
MMP8 + IL4 + C.rectus	0.75
OPG + TNFa + P.intermedia	0.75
MMP8 + OPG + C.rectus	0.75

<u>Signature</u>	<u>AUC</u>
Calprotectin + TNFa + F.nucleatum + C.rectus	0.75
MMP8 + IL2 + F.nucleatum + C.rectus	0.75
IL6 + IL1beta + P.intermedia + C.rectus	0.75
TNFa + P.intermedia	0.75
IL4 + P.intermedia + C.rectus	0.75
Calprotectin + F.nucleatum + C.rectus	0.75
IL13 + TNFa + P.intermedia	0.75
IL10 + IL4 + P.intermedia + C.rectus	0.75
IL2 + IL4 + P.intermedia + C.rectus	0.75
MMP8 + C.rectus	0.75
MMP8 + IL2 + C.rectus	0.75
Calprotectin + IL6 + C.rectus	0.75
IL13 + IL4 + P.intermedia	0.75
IL6 + IL13 + P.intermedia + C.rectus	0.75
IL1beta + IL4 + P.intermedia + C.rectus	0.75
MMP9 + TNFa + F.nucleatum	0.75
OPG + IL4 + P.intermedia + C.rectus	0.75
Calprotectin + IL2 + F.nucleatum + C.rectus	0.74
IL1beta + IL13 + P.intermedia	0.74
IL10 + IL13 + P.intermedia + C.rectus	0.74
IL6 + IL13 + P.intermedia	0.74
IL6 + P.intermedia + C.rectus	0.74
MMP8 + Calprotectin	0.74
IL6 + IL2 + P.intermedia + C.rectus	0.74
IL10 + P.intermedia + C.rectus	0.74
MMP8 + TNFa + F.nucleatum	0.74
MMP9 + ICTP + F.nucleatum	0.74
MMP8 + ICTP	0.74
IL10 + IL2 + P.intermedia + C.rectus	0.74
Calprotectin + IL10 + C.rectus	0.74
IL6 + IL4 + P.intermedia	0.74
IL6 + IL10 + P.intermedia + C.rectus	0.74
IL1beta + P.intermedia + C.rectus	0.74
IL6 + IL1beta + P.intermedia	0.74
IL10 + IL13 + P.intermedia	0.74
IL13 + P.intermedia + C.rectus	0.74
OPG + IL4 + P.intermedia	0.74
IL2 + IL13 + P.intermedia + C.rectus	0.74
P.intermedia + C.rectus	0.74
OPG + IL2 + P.intermedia + C.rectus	0.74
IL10 + IL4 + P.intermedia	0.74
OPG + IL1beta + P.intermedia + C.rectus	0.74
OPG + IL10 + P.intermedia + C.rectus	0.74
OPG + IL13 + P.intermedia + C.rectus	0.74
IL1beta + IL4 + P.intermedia	0.74

<u>Signature</u>	<u>AUC</u>
IL1beta + IL10 + P.intermedia + C.rectus	0.74
Calprotectin + ICTP + C.rectus	0.74
IL2 + IL13 + P.intermedia	0.74
IL1beta + IL13 + P.intermedia + C.rectus	0.74
IL1beta + IL2 + P.intermedia + C.rectus	0.74
IL2 + P.intermedia + C.rectus	0.74
OPG + IL1beta + P.intermedia	0.74
OPG + P.intermedia + C.rectus	0.74
MMP8 + IL10 + F.nucleatum	0.74
OPG + IL13 + P.intermedia	0.74
IL4 + P.intermedia	0.73
MMP9 + IL10 + F.nucleatum	0.73
IL1beta + IL10 + P.intermedia	0.73
IL13 + P.intermedia	0.73
IL2 + IL4 + P.intermedia	0.73
IL1beta + P.intermedia	0.73
MMP8 + OPG + F.nucleatum	0.73
MMP8 + IL1beta + F.nucleatum	0.73
IL1beta + IL2 + P.intermedia	0.73
MMP9 + TNFa	0.73
MMP9 + ICTP	0.73
MMP8 + IL4 + F.nucleatum	0.73
IL6 + P.intermedia	0.73
MMP9 + IL1beta + F.nucleatum	0.73
OPG + IL6 + P.intermedia + C.rectus	0.73
OPG + IL2 + P.intermedia	0.73
IL6 + ICTP + F.nucleatum + C.rectus	0.73
IL6 + IL2 + P.intermedia	0.73
MMP9 + IL4 + F.nucleatum	0.73
OPG + IL10 + P.intermedia	0.73
Calprotectin + IL1beta + C.rectus	0.73
MMP8 + IL2 + F.nucleatum	0.73
Calprotectin + IL4 + C.rectus	0.73
MMP8 + IL6 + F.nucleatum	0.73
MMP9 + OPG + F.nucleatum	0.73
OPG + IL6 + P.intermedia	0.73
OPG + P.intermedia	0.73
IL10 + IL2 + P.intermedia	0.73
IL6 + IL10 + P.intermedia	0.73
MMP8 + TNFa	0.73
MMP8 + MMP9 + F.nucleatum	0.73
MMP8 + IL13 + F.nucleatum	0.73
MMP9 + IL6 + F.nucleatum	0.73
MMP9 + IL13 + F.nucleatum	0.73
MMP8 + OPG	0.72

<u>Signature</u>	<u>AUC</u>
IL2 + P.intermedia	0.72
IL10 + P.intermedia	0.72
P.intermedia	0.72
MMP9 + F.nucleatum	0.72
MMP8 + F.nucleatum	0.72
MMP9 + OPG	0.72
MMP9 + IL2 + F.nucleatum	0.72
IL6 + ICTP + C.rectus	0.72
MMP8 + IL1beta	0.72
Calprotectin + OPG + F.nucleatum	0.72
Calprotectin + IL13 + C.rectus	0.72
MMP8 + MMP9	0.72
MMP8 + IL10	0.71
MMP9 + IL1beta	0.71
IL4 + TNFa + F.nucleatum + C.rectus	0.71
ICTP + IL1beta + F.nucleatum + C.rectus	0.71
MMP9 + IL6	0.71
MMP8 + IL4	0.71
MMP9 + IL4	0.71
MMP8 + IL6	0.71
MMP8 + IL2	0.71
MMP9 + IL10	0.70
ICTP + IL4 + F.nucleatum + C.rectus	0.70
Calprotectin + TNFa + C.rectus	0.70
MMP9 + IL2	0.70
ICTP + TNFa + F.nucleatum + C.rectus	0.70
ICTP + IL10 + F.nucleatum + C.rectus	0.70
IL6 + IL4 + F.nucleatum + C.rectus	0.70
MMP9 + IL13	0.70
MMP8 + IL13	0.70
Calprotectin + IL2 + C.rectus	0.70
Calprotectin + IL6 + F.nucleatum	0.70
Calprotectin + C.rectus	0.70
IL6 + TNFa + F.nucleatum + C.rectus	0.70
ICTP + IL13 + F.nucleatum + C.rectus	0.70
MMP8	0.70
MMP9	0.70

Table 2. Biomarker combinations resulting in an AUC (probability) value great than at least 80%.

<u>Signature</u>	<u>AUC</u>
T.denticola + TNFa + P.intermedia	0.89
Calprotectin + MMP9 + P.gingivalis	0.89
MMP8 + T.forsythia + IL1beta + F.nucleatum	0.89
MMP9 + OPG + P.gingivalis + T.forsythia	0.89
MMP9 + P.gingivalis + T.denticola + IL10	0.89
MMP9 + T.forsythia + ICTP + C.rectus	0.89
MMP9 + OPG + T.denticola	0.89
MMP8 + P.gingivalis + ICTP + F.nucleatum	0.89
Calprotectin + P.gingivalis + IL6 + P.intermedia	0.89
Calprotectin + T.forsythia + IL4 + P.intermedia	0.89
T.forsythia + T.denticola + C.rectus	0.89
Calprotectin + MMP9 + T.denticola	0.89
MMP9 + T.denticola + IL1beta	0.89
T.denticola + ICTP + IL13	0.89
Calprotectin + MMP9 + T.forsythia + F.nucleatum	0.89
Calprotectin + T.forsythia + IL10 + P.intermedia	0.89
MMP9 + T.forsythia + IL6 + P.intermedia	0.89
OPG + T.denticola + IL6 + C.rectus	0.89
T.forsythia + T.denticola + IL10 + IL13	0.89
T.forsythia + ICTP + IL13 + P.intermedia	0.89
T.denticola + IL6 + IL1beta + P.intermedia	0.89
T.denticola + IL6 + TNFa + C.rectus	0.89
T.denticola + IL1beta + TNFa + P.intermedia	0.89
T.denticola + IL4 + TNFa + P.intermedia	0.89
T.denticola + IL4 + P.intermedia	0.89
Calprotectin + MMP9 + P.gingivalis + F.nucleatum	0.89
MMP8 + OPG + P.gingivalis + T.forsythia	0.89
MMP8 + T.denticola + IL2 + F.nucleatum	0.89
OPG + T.denticola + IL10 + P.intermedia	0.89
T.denticola + IL1beta + IL2 + P.intermedia	0.89
MMP9 + P.gingivalis + IL10 + P.intermedia	0.89
MMP9 + T.denticola + IL10 + F.nucleatum	0.89
OPG + T.denticola + IL2 + P.intermedia	0.89
T.denticola + IL6 + IL4 + C.rectus	0.89
T.denticola + IL1beta + IL4 + P.intermedia	0.89
T.denticola + ICTP + IL2	0.89
MMP8 + Calprotectin + P.gingivalis + C.rectus	0.89
Calprotectin + T.forsythia + P.intermedia	0.89
MMP9 + T.forsythia + P.intermedia	0.89
MMP8 + Calprotectin + T.denticola	0.89
MMP8 + Calprotectin + T.forsythia + F.nucleatum	0.89
MMP8 + T.forsythia + ICTP + F.nucleatum	0.89

<u>Signature</u>	<u>AUC</u>
MMP8 + T.denticola + IL10 + F.nucleatum	0.89
Calprotectin + T.forsythia + IL2 + P.intermedia	0.89
MMP9 + T.forsythia + IL1beta + C.rectus	0.89
OPG + T.denticola + IL10 + C.rectus	0.89
P.gingivalis + T.forsythia + P.intermedia	0.89
T.denticola + ICTP + TNFa	0.89
MMP8 + Calprotectin + T.forsythia + C.rectus	0.89
Calprotectin + T.forsythia + IL6 + P.intermedia	0.89
Calprotectin + T.forsythia + IL6 + C.rectus	0.89
T.forsythia + IL13 + TNFa + P.intermedia	0.89
T.denticola + IL1beta + IL10 + P.intermedia	0.89
T.denticola + IL6 + IL2 + C.rectus	0.89
MMP8 + MMP9 + P.gingivalis + T.forsythia	0.89
T.denticola + IL6 + IL1beta + C.rectus	0.89
MMP9 + T.forsythia + IL1beta + F.nucleatum	0.89
OPG + T.forsythia + T.denticola + IL13	0.89
T.forsythia + ICTP + IL1beta + P.intermedia	0.89
T.denticola + IL6 + P.intermedia	0.89
T.denticola + IL6 + C.rectus	0.89
MMP9 + T.denticola + IL2 + F.nucleatum	0.89
P.gingivalis + IL6 + ICTP + P.intermedia	0.89
T.forsythia + ICTP + TNFa + P.intermedia	0.89
T.denticola + IL6 + IL10 + P.intermedia	0.89
T.denticola + IL6 + IL10 + C.rectus	0.89
T.denticola + IL1beta + P.intermedia	0.89
MMP9 + T.denticola + TNFa + F.nucleatum	0.89
T.forsythia + ICTP + IL4 + P.intermedia	0.89
MMP8 + T.denticola + IL13 + F.nucleatum	0.89
MMP8 + T.denticola + TNFa + F.nucleatum	0.89
MMP8 + MMP9 + T.denticola + F.nucleatum	0.89
Calprotectin + T.forsythia + ICTP + C.rectus	0.89
MMP9 + T.denticola + IL6 + F.nucleatum	0.89
MMP9 + T.denticola + IL13 + F.nucleatum	0.89
MMP9 + T.denticola + IL4 + F.nucleatum	0.89
MMP8 + P.gingivalis + ICTP + C.rectus	0.89
OPG + T.denticola + IL13 + C.rectus	0.89
T.denticola + IL10 + IL2 + P.intermedia	0.89
T.denticola + IL10 + IL13 + C.rectus	0.89
MMP8 + T.denticola + IL2	0.89
MMP8 + T.denticola + IL6 + F.nucleatum	0.89
Calprotectin + OPG + T.denticola + F.nucleatum	0.89
OPG + T.forsythia + T.denticola + TNFa	0.89
T.forsythia + T.denticola + IL2 + IL13	0.89
T.forsythia + IL6 + IL13 + P.intermedia	0.89
MMP8 + T.denticola + F.nucleatum	0.89

<u>Signature</u>	<u>AUC</u>
MMP9 + T.denticola + F.nucleatum	0.89
MMP9 + T.denticola + TNFa	0.89
MMP9 + P.gingivalis + ICTP + C.rectus	0.89
T.forsythia + IL10 + IL13 + P.intermedia	0.89
T.denticola + IL10 + IL2 + C.rectus	0.89
T.denticola + IL2 + P.intermedia	0.89
MMP8 + T.denticola + IL4 + F.nucleatum	0.89
Calprotectin + OPG + T.forsythia + F.nucleatum	0.89
MMP9 + P.gingivalis + T.forsythia + IL2	0.89
MMP8 + Calprotectin + P.gingivalis	0.89
MMP8 + T.forsythia + TNFa + C.rectus	0.89
MMP8 + T.denticola + IL10	0.89
MMP8 + T.denticola + TNFa	0.89
MMP8 + Calprotectin + P.gingivalis + F.nucleatum	0.89
MMP8 + T.denticola + IL13	0.89
Calprotectin + MMP9 + T.forsythia	0.89
MMP9 + T.denticola + IL13	0.89
MMP9 + T.forsythia + ICTP + F.nucleatum	0.89
MMP9 + T.forsythia + IL2 + C.rectus	0.89
OPG + T.forsythia + T.denticola + IL4	0.89
T.forsythia + ICTP + IL10 + P.intermedia	0.89
T.denticola + ICTP + IL4	0.89
Calprotectin + P.gingivalis + T.forsythia + IL13	0.89
OPG + T.forsythia + T.denticola + IL6	0.89
MMP9 + P.gingivalis + T.forsythia + IL10	0.89
T.denticola + P.intermedia	0.89
T.denticola + ICTP	0.89
MMP8 + P.gingivalis + ICTP	0.89
MMP9 + T.denticola + IL6	0.89
MMP8 + OPG + T.forsythia + C.rectus	0.89
Calprotectin + T.forsythia + T.denticola + IL6	0.89
MMP9 + P.gingivalis + ICTP + F.nucleatum	0.89
MMP9 + T.forsythia + TNFa + F.nucleatum	0.89
T.forsythia + ICTP + IL2 + P.intermedia	0.89
T.denticola + IL1beta + IL10 + C.rectus	0.89
T.denticola + IL10 + IL4 + C.rectus	0.89
P.gingivalis + T.denticola + C.rectus	0.89
MMP9 + T.denticola + IL2	0.89
T.denticola + ICTP + IL1beta	0.89
MMP8 + P.gingivalis + T.forsythia + IL10	0.89
Calprotectin + P.gingivalis + IL6 + C.rectus	0.89
Calprotectin + T.forsythia + T.denticola + IL10	0.89
MMP9 + OPG + T.forsythia + C.rectus	0.89
OPG + T.forsythia + T.denticola + IL1beta	0.89
T.forsythia + IL1beta + IL13 + P.intermedia	0.89

<u>Signature</u>	<u>AUC</u>
T.forsythia + IL2 + IL13 + P.intermedia	0.89
T.denticola + IL10 + TNFa + C.rectus	0.89
T.denticola + IL10 + C.rectus	0.89
MMP8 + MMP9 + T.denticola	0.89
MMP9 + T.denticola + IL10	0.89
MMP8 + T.denticola + IL6	0.89
MMP8 + T.forsythia + TNFa + F.nucleatum	0.89
Calprotectin + T.forsythia + T.denticola + TNFa	0.89
Calprotectin + T.forsythia + ICTP + F.nucleatum	0.89
P.gingivalis + ICTP + IL13 + P.intermedia	0.89
P.gingivalis + IL10 + IL13 + P.intermedia	0.89
T.denticola + IL10 + P.intermedia	0.89
MMP9 + P.gingivalis + T.forsythia + IL6	0.89
OPG + T.forsythia + T.denticola + IL10	0.89
T.forsythia + IL13 + P.intermedia	0.88
MMP8 + P.gingivalis + T.forsythia + IL6	0.88
Calprotectin + T.forsythia + T.denticola + IL1beta	0.88
OPG + T.forsythia + T.denticola + IL2	0.88
P.gingivalis + ICTP + IL1beta + P.intermedia	0.88
T.denticola + IL1beta + IL13 + C.rectus	0.88
Calprotectin + T.forsythia + T.denticola + IL2	0.88
P.gingivalis + ICTP + TNFa + P.intermedia	0.88
MMP9 + T.forsythia + IL4 + C.rectus	0.88
T.forsythia + IL6 + ICTP + P.intermedia	0.88
T.denticola + IL2 + IL13 + C.rectus	0.88
OPG + T.denticola + C.rectus	0.88
MMP9 + T.forsythia + IL13 + F.nucleatum	0.88
MMP9 + T.forsythia + IL13 + C.rectus	0.88
OPG + T.forsythia + ICTP + P.intermedia	0.88
OPG + T.forsythia + T.denticola	0.88
MMP8 + P.gingivalis + T.forsythia + IL2	0.88
OPG + T.forsythia + IL13 + P.intermedia	0.88
T.forsythia + T.denticola + IL13 + IL4	0.88
T.denticola + IL2 + TNFa + C.rectus	0.88
T.forsythia + T.denticola + IL13	0.88
P.gingivalis + ICTP + IL10 + P.intermedia	0.88
T.forsythia + T.denticola + IL1beta + IL13	0.88
T.forsythia + IL13 + IL4 + P.intermedia	0.88
MMP8 + T.denticola + IL4	0.88
MMP9 + T.denticola + IL4	0.88
P.gingivalis + IL1beta + IL13 + P.intermedia	0.88
T.forsythia + P.intermedia + F.nucleatum	0.88
MMP8 + T.forsythia + IL13 + F.nucleatum	0.88
Calprotectin + P.gingivalis + T.forsythia + ICTP	0.88
T.forsythia + T.denticola + IL2 + TNFa	0.88

<u>Signature</u>	<u>AUC</u>
MMP8 + MMP9 + T.forsythia + C.rectus	0.88
MMP8 + T.forsythia + IL13 + C.rectus	0.88
Calprotectin + T.forsythia + T.denticola + IL4	0.88
Calprotectin + T.forsythia + IL13 + F.nucleatum	0.88
OPG + T.denticola + IL1beta + C.rectus	0.88
T.denticola + IL1beta + IL2 + C.rectus	0.88
MMP8 + T.denticola	0.88
MMP9 + T.denticola	0.88
Calprotectin + T.forsythia + T.denticola	0.88
P.gingivalis + ICTP + P.intermedia	0.88
T.denticola + IL2 + C.rectus	0.88
T.denticola + IL2 + IL4 + C.rectus	0.88
MMP8 + P.gingivalis + T.forsythia	0.88
MMP9 + P.gingivalis + T.forsythia	0.88
T.forsythia + ICTP + P.intermedia	0.88
MMP8 + OPG + T.forsythia + F.nucleatum	0.88
MMP8 + T.forsythia + IL4 + C.rectus	0.88
Calprotectin + OPG + P.gingivalis + T.denticola	0.88
OPG + T.denticola + IL2 + C.rectus	0.88
T.forsythia + IL1beta + TNFa + P.intermedia	0.88
P.gingivalis + P.intermedia + F.nucleatum	0.88
P.gingivalis + ICTP + IL2 + P.intermedia	0.88
T.forsythia + IL10 + TNFa + P.intermedia	0.88
T.denticola + F.nucleatum + C.rectus	0.88
Calprotectin + P.gingivalis + T.denticola + IL13	0.88
Calprotectin + T.forsythia + IL1beta + F.nucleatum	0.88
OPG + P.gingivalis + ICTP + P.intermedia	0.88
P.gingivalis + ICTP + IL4 + P.intermedia	0.88
T.forsythia + T.denticola + IL1beta + IL10	0.88
T.forsythia + T.denticola + IL10 + TNFa	0.88
MMP8 + T.forsythia + IL2 + C.rectus	0.88
Calprotectin + T.forsythia + IL13 + C.rectus	0.88
T.forsythia + T.denticola + IL6 + IL4	0.88
T.forsythia + IL6 + TNFa + P.intermedia	0.88
Calprotectin + OPG + P.gingivalis + T.forsythia	0.88
T.forsythia + T.denticola + IL6 + TNFa	0.88
T.forsythia + T.denticola + IL13 + TNFa	0.88
T.denticola + IL13 + IL4 + C.rectus	0.88
T.denticola + IL13 + C.rectus	0.88
MMP8 + T.forsythia + ICTP	0.88
MMP9 + P.gingivalis + ICTP	0.88
MMP9 + T.forsythia + IL6 + C.rectus	0.88
OPG + P.gingivalis + T.denticola + IL13	0.88
OPG + T.forsythia + TNFa + P.intermedia	0.88
P.gingivalis + T.forsythia + IL6 + ICTP	0.88

<u>Signature</u>	<u>AUC</u>
T.forsythia + T.denticola + IL6 + IL1beta	0.88
Calprotectin + P.gingivalis + T.denticola + IL6	0.88
OPG + P.gingivalis + T.denticola + IL10	0.88
T.forsythia + T.denticola + IL1beta + IL2	0.88
T.forsythia + T.denticola + F.nucleatum	0.88
MMP8 + T.forsythia + IL1beta	0.88
MMP9 + T.forsythia + TNFa + C.rectus	0.88
Calprotectin + P.gingivalis + ICTP + F.nucleatum	0.88
MMP9 + T.forsythia + IL10 + C.rectus	0.88
OPG + T.denticola + IL4 + C.rectus	0.88
T.forsythia + T.denticola + IL2 + IL4	0.88
MMP9 + T.forsythia + C.rectus	0.88
MMP9 + T.forsythia + ICTP	0.88
OPG + P.gingivalis + T.denticola + IL6	0.88
OPG + T.denticola + TNFa + C.rectus	0.88
P.gingivalis + T.denticola + IL10 + IL13	0.88
T.forsythia + IL2 + TNFa + P.intermedia	0.88
T.denticola + IL13 + TNFa + C.rectus	0.88
T.denticola + IL4 + TNFa + C.rectus	0.88
MMP8 + Calprotectin + T.forsythia	0.88
T.forsythia + IL1beta + IL10 + P.intermedia	0.88
T.forsythia + IL4 + TNFa + P.intermedia	0.88
Calprotectin + OPG + P.gingivalis + C.rectus	0.88
T.forsythia + T.denticola + IL6 + IL2	0.88
T.forsythia + T.denticola + IL1beta + TNFa	0.88
T.denticola + IL1beta + IL4 + C.rectus	0.88
T.forsythia + TNFa + P.intermedia	0.88
Calprotectin + T.denticola + IL6 + F.nucleatum	0.88
P.gingivalis + T.forsythia + IL6 + IL13	0.88
T.denticola + IL4 + C.rectus	0.88
P.gingivalis + IL6 + IL13 + P.intermedia	0.88
MMP8 + OPG + T.forsythia	0.88
MMP9 + OPG + T.forsythia	0.88
Calprotectin + T.forsythia + TNFa + F.nucleatum	0.88
MMP9 + T.forsythia + IL4 + F.nucleatum	0.88
OPG + P.gingivalis + T.denticola + IL4	0.88
P.gingivalis + IL6 + TNFa + P.intermedia	0.88
T.denticola + TNFa + C.rectus	0.88
MMP9 + T.forsythia + IL1beta	0.88
MMP9 + T.forsythia + TNFa	0.88
Calprotectin + T.forsythia + IL1beta + C.rectus	0.88
MMP9 + P.gingivalis + IL6 + F.nucleatum	0.88
MMP9 + P.gingivalis + IL10 + F.nucleatum	0.88
P.gingivalis + T.denticola + IL6 + IL13	0.88
T.forsythia + T.denticola + IL1beta + IL4	0.88

<u>Signature</u>	<u>AUC</u>
T.forsythia + IL6 + IL10 + P.intermedia	0.88
T.forsythia + IL6 + IL13 + C.rectus	0.88
T.denticola + IL1beta + TNFa + C.rectus	0.88
T.denticola + C.rectus	0.88
T.forsythia + T.denticola + TNFa	0.88
T.denticola + IL1beta + C.rectus	0.88
MMP8 + P.gingivalis + IL10 + F.nucleatum	0.88
MMP8 + T.forsythia + IL10 + C.rectus	0.88
MMP9 + P.gingivalis + IL6 + C.rectus	0.88
MMP9 + P.gingivalis + TNFa + C.rectus	0.88
T.forsythia + T.denticola + IL10 + IL4	0.88
T.forsythia + IL6 + IL1beta + P.intermedia	0.88
T.forsythia + T.denticola + IL1beta	0.88
MMP9 + T.forsythia + IL13	0.88
MMP8 + T.forsythia + IL6 + C.rectus	0.88
Calprotectin + P.gingivalis + T.forsythia + IL6	0.88
Calprotectin + T.forsythia + TNFa + C.rectus	0.88
MMP9 + T.forsythia + IL2 + F.nucleatum	0.88
OPG + P.gingivalis + T.denticola + IL1beta	0.88
OPG + P.gingivalis + T.denticola + IL2	0.88
T.forsythia + IL6 + ICTP + C.rectus	0.88
MMP8 + P.gingivalis + IL1beta + F.nucleatum	0.88
MMP9 + OPG + P.gingivalis + C.rectus	0.88
OPG + P.gingivalis + IL13 + P.intermedia	0.88
OPG + T.forsythia + IL1beta + P.intermedia	0.88
T.forsythia + T.denticola + IL4 + TNFa	0.88
MMP8 + T.forsythia + IL13	0.88
MMP8 + MMP9 + P.gingivalis + C.rectus	0.88
MMP8 + T.forsythia + IL4 + F.nucleatum	0.88
Calprotectin + T.forsythia + IL10 + C.rectus	0.88
Calprotectin + T.denticola + IL2 + F.nucleatum	0.88
P.gingivalis + T.denticola + IL2 + IL13	0.88
P.gingivalis + IL13 + IL4 + P.intermedia	0.88
OPG + P.gingivalis + T.denticola	0.88
MMP8 + T.forsythia + IL6 + F.nucleatum	0.88
MMP9 + T.forsythia + IL6 + F.nucleatum	0.88
P.gingivalis + T.denticola + IL1beta + IL13	0.88
P.gingivalis + IL6 + IL4 + P.intermedia	0.88
T.forsythia + T.denticola + IL10 + IL2	0.88
MMP8 + T.forsythia + C.rectus	0.88
T.forsythia + T.denticola + IL6	0.88
Calprotectin + OPG + P.gingivalis + F.nucleatum	0.88
Calprotectin + T.forsythia + IL6 + F.nucleatum	0.88
OPG + T.forsythia + IL2 + P.intermedia	0.88
P.gingivalis + IL6 + ICTP + F.nucleatum	0.88

<u>Signature</u>	<u>AUC</u>
P.gingivalis + IL6 + IL1beta + P.intermedia	0.88
Calprotectin + T.forsythia + IL4 + F.nucleatum	0.87
MMP9 + P.gingivalis + IL1beta + F.nucleatum	0.87
MMP9 + P.gingivalis + IL4 + C.rectus	0.87
OPG + T.forsythia + IL6 + P.intermedia	0.87
T.forsythia + T.denticola + IL6 + IL10	0.87
T.forsythia + IL10 + IL4 + P.intermedia	0.87
P.gingivalis + IL13 + P.intermedia	0.87
MMP8 + T.forsythia + TNFa	0.87
MMP9 + P.gingivalis + TNFa + F.nucleatum	0.87
OPG + P.gingivalis + T.forsythia + IL6	0.87
OPG + P.gingivalis + T.denticola + TNFa	0.87
P.gingivalis + IL2 + IL13 + P.intermedia	0.87
T.forsythia + IL6 + IL13 + F.nucleatum	0.87
Calprotectin + T.denticola + IL10 + F.nucleatum	0.87
MMP9 + P.gingivalis + IL13 + C.rectus	0.87
T.forsythia + IL10 + IL2 + P.intermedia	0.87
T.forsythia + T.denticola + IL4	0.87
T.forsythia + IL10 + P.intermedia	0.87
MMP8 + OPG + P.gingivalis + C.rectus	0.87
Calprotectin + T.forsythia + IL2 + C.rectus	0.87
MMP9 + P.gingivalis + IL10 + C.rectus	0.87
T.forsythia + ICTP + IL13 + F.nucleatum	0.87
MMP9 + T.forsythia + F.nucleatum	0.87
MMP8 + OPG + P.gingivalis + F.nucleatum	0.87
MMP8 + P.gingivalis + IL6 + F.nucleatum	0.87
Calprotectin + T.denticola + IL13 + F.nucleatum	0.87
MMP9 + OPG + T.forsythia + F.nucleatum	0.87
MMP9 + P.gingivalis + IL2 + C.rectus	0.87
P.gingivalis + T.denticola + IL13 + IL4	0.87
Calprotectin + T.forsythia + C.rectus	0.87
P.gingivalis + IL6 + P.intermedia	0.87
Calprotectin + P.gingivalis + T.denticola + IL10	0.87
Calprotectin + T.forsythia + IL4 + C.rectus	0.87
OPG + T.forsythia + IL10 + P.intermedia	0.87
P.gingivalis + IL6 + IL10 + P.intermedia	0.87
P.gingivalis + IL6 + IL2 + P.intermedia	0.87
MMP8 + T.forsythia + F.nucleatum	0.87
T.forsythia + IL1beta + P.intermedia	0.87
MMP8 + T.forsythia + IL2 + F.nucleatum	0.87
Calprotectin + T.denticola + TNFa + F.nucleatum	0.87
MMP9 + T.forsythia + IL10 + F.nucleatum	0.87
OPG + P.gingivalis + IL6 + P.intermedia	0.87
OPG + T.forsythia + IL4 + P.intermedia	0.87
P.gingivalis + T.denticola + IL13 + TNFa	0.87

<u>Signature</u>	<u>AUC</u>
T.forsythia + IL1beta + IL2 + P.intermedia	0.87
T.forsythia + IL1beta + IL4 + P.intermedia	0.87
MMP8 + MMP9 + T.forsythia + F.nucleatum	0.87
MMP8 + P.gingivalis + TNFa + C.rectus	0.87
P.gingivalis + IL6 + ICTP + C.rectus	0.87
T.forsythia + T.denticola + IL10	0.87
T.forsythia + T.denticola + IL2	0.87
Calprotectin + P.gingivalis + T.denticola + IL2	0.87
Calprotectin + P.gingivalis + IL6 + F.nucleatum	0.87
P.gingivalis + IL1beta + IL10 + P.intermedia	0.87
T.forsythia + ICTP + IL13 + C.rectus	0.87
MMP8 + P.gingivalis + IL4 + C.rectus	0.87
P.gingivalis + T.forsythia + IL6 + TNFa	0.87
P.gingivalis + T.forsythia + ICTP + IL13	0.87
T.forsythia + IL6 + IL4 + P.intermedia	0.87
MMP8 + P.gingivalis + IL1beta + C.rectus	0.87
MMP8 + T.forsythia + IL10 + F.nucleatum	0.87
MMP9 + P.gingivalis + IL1beta + C.rectus	0.87
P.gingivalis + IL13 + TNFa + P.intermedia	0.87
T.forsythia + P.intermedia + C.rectus	0.87
OPG + T.forsythia + P.intermedia	0.87
MMP9 + P.gingivalis + IL4 + F.nucleatum	0.87
T.denticola + IL6 + IL13 + F.nucleatum	0.87
MMP9 + P.gingivalis + C.rectus	0.87
OPG + P.gingivalis + TNFa + P.intermedia	0.87
T.forsythia + ICTP + TNFa + F.nucleatum	0.87
MMP9 + OPG + P.gingivalis	0.87
MMP9 + P.gingivalis + IL1beta	0.87
MMP8 + P.gingivalis + IL10 + C.rectus	0.87
Calprotectin + T.denticola + IL4 + F.nucleatum	0.87
OPG + T.denticola + IL13 + F.nucleatum	0.87
MMP9 + P.gingivalis + IL6	0.87
P.gingivalis + IL1beta + TNFa + P.intermedia	0.87
T.forsythia + IL6 + IL2 + P.intermedia	0.87
T.denticola + IL10 + IL13 + F.nucleatum	0.87
T.denticola + IL2 + TNFa + F.nucleatum	0.87
MMP8 + MMP9 + P.gingivalis + F.nucleatum	0.87
Calprotectin + P.gingivalis + ICTP + C.rectus	0.87
OPG + T.denticola + IL6 + F.nucleatum	0.87
T.forsythia + IL4 + P.intermedia	0.87
MMP8 + OPG + P.gingivalis	0.87
MMP8 + P.gingivalis + IL6	0.87
MMP8 + P.gingivalis + IL10	0.87
MMP8 + P.gingivalis + TNFa + F.nucleatum	0.87
OPG + P.gingivalis + IL1beta + P.intermedia	0.87

<u>Signature</u>	<u>AUC</u>
OPG + P.gingivalis + IL4 + P.intermedia	0.87
P.gingivalis + T.forsythia + IL10 + IL13	0.87
P.gingivalis + IL1beta + IL2 + P.intermedia	0.87
P.gingivalis + IL1beta + IL4 + P.intermedia	0.87
T.forsythia + IL6 + ICTP + F.nucleatum	0.87
MMP9 + P.gingivalis + F.nucleatum	0.87
OPG + P.gingivalis + P.intermedia	0.87
MMP8 + P.gingivalis + IL1beta	0.87
T.forsythia + IL6 + P.intermedia	0.87
MMP8 + T.forsythia + IL4	0.87
MMP9 + T.forsythia + IL4	0.87
MMP8 + P.gingivalis + IL13 + C.rectus	0.87
Calprotectin + T.denticola + IL1beta + F.nucleatum	0.87
MMP9 + P.gingivalis + IL13 + F.nucleatum	0.87
P.gingivalis + T.forsythia + IL6 + IL4	0.87
P.gingivalis + IL10 + TNFa + P.intermedia	0.87
Calprotectin + T.denticola + F.nucleatum	0.87
P.gingivalis + T.denticola + IL13	0.87
Calprotectin + OPG + T.denticola	0.87
P.gingivalis + IL1beta + P.intermedia	0.87
P.gingivalis + TNFa + P.intermedia	0.87
Calprotectin + P.gingivalis + T.forsythia + IL10	0.87
Calprotectin + P.gingivalis + IL10 + C.rectus	0.87
P.gingivalis + T.forsythia + ICTP + IL10	0.87
P.gingivalis + IL4 + TNFa + P.intermedia	0.87
P.gingivalis + T.forsythia + C.rectus	0.87
Calprotectin + P.gingivalis + T.denticola	0.87
MMP9 + P.gingivalis + TNFa	0.87
OPG + P.gingivalis + IL10 + P.intermedia	0.87
OPG + P.gingivalis + IL2 + P.intermedia	0.87
MMP8 + P.gingivalis + F.nucleatum	0.87
P.gingivalis + IL2 + P.intermedia	0.87
MMP8 + P.gingivalis + IL6 + C.rectus	0.87
MMP8 + P.gingivalis + IL4 + F.nucleatum	0.87
Calprotectin + P.gingivalis + T.denticola + IL1beta	0.87
Calprotectin + T.forsythia + IL2 + F.nucleatum	0.87
OPG + P.gingivalis + T.forsythia + ICTP	0.87
P.gingivalis + T.denticola + IL6 + IL1beta	0.87
P.gingivalis + T.denticola + IL6 + IL2	0.87
P.gingivalis + IL2 + IL4 + P.intermedia	0.87
P.gingivalis + IL2 + TNFa + P.intermedia	0.87
P.gingivalis + P.intermedia + C.rectus	0.87
MMP8 + P.gingivalis + TNFa	0.87
MMP8 + P.gingivalis + IL2 + F.nucleatum	0.87
OPG + T.denticola + IL10 + F.nucleatum	0.87

<u>Signature</u>	<u>AUC</u>
P.gingivalis + IL10 + IL2 + P.intermedia	0.87
T.denticola + IL2 + IL13 + F.nucleatum	0.87
MMP8 + P.gingivalis + C.rectus	0.87
Calprotectin + T.forsythia + F.nucleatum	0.87
P.gingivalis + IL4 + P.intermedia	0.87
Calprotectin + P.gingivalis + T.denticola + TNFa	0.87
MMP9 + P.gingivalis + IL2 + F.nucleatum	0.87
P.gingivalis + T.forsythia + IL6 + IL1beta	0.87
T.forsythia + T.denticola	0.87
P.gingivalis + T.denticola + IL10 + IL2	0.87
T.forsythia + IL2 + P.intermedia	0.87
MMP8 + P.gingivalis + IL13 + F.nucleatum	0.87
OPG + T.denticola + IL2 + F.nucleatum	0.87
P.gingivalis + T.denticola + IL6 + IL10	0.87
P.gingivalis + T.denticola + IL6 + TNFa	0.87
MMP9 + OPG + P.gingivalis + F.nucleatum	0.87
T.forsythia + IL2 + IL4 + P.intermedia	0.87
P.gingivalis + T.forsythia + T.denticola	0.87
MMP8 + MMP9 + P.gingivalis	0.87
OPG + T.denticola + TNFa + F.nucleatum	0.87
P.gingivalis + T.denticola + IL6 + IL4	0.87
P.gingivalis + T.denticola + IL2 + TNFa	0.87
T.forsythia + IL10 + IL13 + F.nucleatum	0.87
MMP9 + P.gingivalis + IL13	0.87
Calprotectin + T.forsythia + IL10 + F.nucleatum	0.87
P.gingivalis + T.forsythia + IL6 + IL10	0.87
P.gingivalis + P.intermedia	0.87
T.forsythia + P.intermedia	0.87
P.gingivalis + T.forsythia + IL6	0.87
P.gingivalis + T.denticola + IL6	0.87
MMP9 + P.gingivalis + IL10	0.87
Calprotectin + P.gingivalis + T.denticola + IL4	0.87
Calprotectin + P.gingivalis + IL10 + F.nucleatum	0.87
OPG + T.denticola + IL1beta + F.nucleatum	0.87
P.gingivalis + IL10 + IL4 + P.intermedia	0.87
T.forsythia + ICTP + IL10 + C.rectus	0.87
P.gingivalis + IL10 + P.intermedia	0.86
MMP8 + P.gingivalis + IL4	0.86
MMP9 + P.gingivalis + IL4	0.86
P.gingivalis + T.denticola + IL10 + TNFa	0.86
P.gingivalis + T.forsythia + F.nucleatum	0.86
MMP9 + T.forsythia + IL2	0.86
P.gingivalis + T.forsythia + IL6 + IL2	0.86
MMP9 + T.forsythia + IL10	0.86
P.gingivalis + T.denticola + IL1beta + IL10	0.86

<u>Signature</u>	<u>AUC</u>
P.gingivalis + T.denticola + IL1beta + IL2	0.86
T.forsythia + IL6 + TNFa + C.rectus	0.86
P.gingivalis + T.denticola + IL10	0.86
MMP8 + P.gingivalis + IL13	0.86
Calprotectin + P.gingivalis + T.forsythia + IL4	0.86
OPG + T.forsythia + IL13 + F.nucleatum	0.86
P.gingivalis + T.denticola + F.nucleatum	0.86
MMP8 + MMP9 + T.forsythia	0.86
Calprotectin + T.denticola + IL6	0.86
MMP9 + T.forsythia + IL6	0.86
MMP8 + P.gingivalis + IL2 + C.rectus	0.86
Calprotectin + P.gingivalis + T.forsythia + TNFa	0.86
OPG + P.gingivalis + T.forsythia + IL10	0.86
T.forsythia + IL6 + TNFa + F.nucleatum	0.86
T.denticola + IL6 + IL10 + F.nucleatum	0.86
P.gingivalis + T.denticola + IL2	0.86
Calprotectin + P.gingivalis + T.forsythia + IL2	0.86
OPG + T.forsythia + ICTP + F.nucleatum	0.86
OPG + T.forsythia + ICTP + C.rectus	0.86
P.gingivalis + T.denticola + IL10 + IL4	0.86
T.denticola + IL6 + IL1beta + F.nucleatum	0.86
MMP8 + T.forsythia + IL6	0.86
Calprotectin + OPG + T.forsythia	0.86
Calprotectin + P.gingivalis + IL4 + C.rectus	0.86
P.gingivalis + T.forsythia + ICTP + IL2	0.86
P.gingivalis + T.denticola + IL2 + IL4	0.86
T.forsythia + ICTP + IL2 + F.nucleatum	0.86
P.gingivalis + T.forsythia + ICTP + IL4	0.86
P.gingivalis + T.forsythia + IL1beta + IL13	0.86
Calprotectin + T.forsythia + ICTP	0.86
Calprotectin + T.forsythia + IL13	0.86
Calprotectin + P.gingivalis + IL2 + C.rectus	0.86
P.gingivalis + T.forsythia + ICTP + TNFa	0.86
T.denticola + IL13 + IL4 + F.nucleatum	0.86
MMP8 + T.forsythia + IL2	0.86
T.denticola + IL6 + TNFa + F.nucleatum	0.86
Calprotectin + P.gingivalis + T.forsythia	0.86
OPG + T.denticola + F.nucleatum	0.86
MMP8 + T.forsythia + IL10	0.86
T.denticola + IL6 + IL13	0.86
OPG + T.denticola + IL4 + F.nucleatum	0.86
MMP8 + P.gingivalis + IL2	0.86
Calprotectin + T.denticola + IL13	0.86
OPG + T.denticola + IL6	0.86
Calprotectin + P.gingivalis + T.forsythia + IL1beta	0.86

<u>Signature</u>	<u>AUC</u>
T.forsythia + IL6 + IL1beta + F.nucleatum	0.86
T.forsythia + ICTP + IL4 + F.nucleatum	0.86
T.forsythia + IL2 + IL13 + F.nucleatum	0.86
T.denticola + IL1beta + IL10 + F.nucleatum	0.86
Calprotectin + P.gingivalis + TNFa + C.rectus	0.86
OPG + T.forsythia + TNFa + F.nucleatum	0.86
T.forsythia + ICTP + IL1beta + F.nucleatum	0.86
T.denticola + IL10 + TNFa + F.nucleatum	0.86
P.gingivalis + T.forsythia + ICTP	0.86
Calprotectin + P.gingivalis + IL1beta + C.rectus	0.86
OPG + P.gingivalis + T.forsythia + IL13	0.86
T.forsythia + ICTP + IL10 + F.nucleatum	0.86
T.forsythia + ICTP + TNFa + C.rectus	0.86
T.denticola + IL6 + IL2 + F.nucleatum	0.86
T.forsythia + ICTP + F.nucleatum	0.86
T.forsythia + IL1beta + IL13 + F.nucleatum	0.86
MMP8 + P.gingivalis	0.86
MMP9 + P.gingivalis	0.86
P.gingivalis + T.denticola + IL4	0.86
T.denticola + IL6 + F.nucleatum	0.86
Calprotectin + T.forsythia + IL6	0.86
OPG + T.forsythia + IL6 + F.nucleatum	0.86
T.forsythia + IL10 + IL13 + C.rectus	0.86
MMP8 + T.forsythia	0.86
MMP9 + T.forsythia	0.86
T.forsythia + IL6 + IL13	0.86
T.forsythia + ICTP + IL4 + C.rectus	0.86
Calprotectin + T.denticola + IL10	0.86
P.gingivalis + T.forsythia + IL2 + IL13	0.86
P.gingivalis + T.forsythia + IL13 + TNFa	0.86
T.forsythia + IL6 + IL4 + C.rectus	0.86
T.forsythia + ICTP + IL1beta + C.rectus	0.86
Calprotectin + P.gingivalis + IL6	0.86
P.gingivalis + T.forsythia + ICTP + IL1beta	0.86
T.denticola + IL1beta + IL2 + F.nucleatum	0.86
T.denticola + IL1beta + IL13 + F.nucleatum	0.86
P.gingivalis + T.denticola + IL4 + TNFa	0.86
T.forsythia + IL13 + IL4 + F.nucleatum	0.86
T.denticola + IL6 + IL4 + F.nucleatum	0.86
T.forsythia + IL6 + IL1beta + C.rectus	0.86
T.forsythia + IL6 + IL10 + C.rectus	0.86
Calprotectin + T.denticola + IL2	0.86
OPG + P.gingivalis + T.forsythia + IL2	0.86
T.forsythia + IL6 + IL2 + C.rectus	0.86
MMP9 + P.gingivalis + IL2	0.86

<u>Signature</u>	<u>AUC</u>
P.gingivalis + T.denticola + IL1beta + IL4	0.86
T.forsythia + ICTP + IL2 + C.rectus	0.86
Calprotectin + P.gingivalis + IL13 + F.nucleatum	0.86
T.forsythia + ICTP + C.rectus	0.86
T.forsythia + ICTP + IL13	0.86
P.gingivalis + IL6 + TNFa + F.nucleatum	0.86
T.forsythia + IL6 + IL4 + F.nucleatum	0.86
T.denticola + IL2 + IL4 + F.nucleatum	0.86
T.denticola + IL2 + F.nucleatum	0.86
T.denticola + IL10 + IL13	0.86
OPG + P.gingivalis + T.forsythia + IL4	0.86
OPG + T.forsythia + IL6 + C.rectus	0.86
P.gingivalis + IL6 + IL13 + F.nucleatum	0.86
Calprotectin + P.gingivalis + C.rectus	0.86
Calprotectin + P.gingivalis + ICTP	0.86
P.gingivalis + T.denticola	0.86
P.gingivalis + T.denticola + TNFa	0.86
Calprotectin + P.gingivalis + TNFa + F.nucleatum	0.86
P.gingivalis + IL10 + IL13 + F.nucleatum	0.86
OPG + P.gingivalis + T.forsythia	0.86
P.gingivalis + T.forsythia + IL13	0.86
T.denticola + IL13 + F.nucleatum	0.86
P.gingivalis + IL6 + ICTP	0.86
OPG + P.gingivalis + T.forsythia + TNFa	0.86
P.gingivalis + T.forsythia + IL13 + IL4	0.86
P.gingivalis + ICTP + IL10 + F.nucleatum	0.86
T.denticola + IL10 + F.nucleatum	0.86
OPG + T.denticola + IL13	0.86
Calprotectin + P.gingivalis + IL2 + F.nucleatum	0.86
Calprotectin + P.gingivalis + IL4 + F.nucleatum	0.86
T.forsythia + IL13 + TNFa + F.nucleatum	0.86
T.denticola + IL13 + TNFa + F.nucleatum	0.86
Calprotectin + P.gingivalis + F.nucleatum	0.86
Calprotectin + T.denticola + IL4	0.86
OPG + T.denticola + IL10	0.86
Calprotectin + P.gingivalis + IL13 + C.rectus	0.86
T.denticola + IL10 + IL4 + F.nucleatum	0.86
P.gingivalis + T.forsythia + IL10	0.85
P.gingivalis + T.denticola + IL1beta	0.85
P.gingivalis + T.denticola + IL1beta + TNFa	0.85
OPG + T.forsythia + IL4 + C.rectus	0.85
OPG + T.forsythia + IL1beta + C.rectus	0.85
OPG + T.forsythia + IL13 + C.rectus	0.85
P.gingivalis + T.forsythia + IL10 + IL2	0.85
T.forsythia + IL10 + TNFa + F.nucleatum	0.85

<u>Signature</u>	<u>AUC</u>
Calprotectin + T.denticola + TNFa	0.85
T.forsythia + F.nucleatum + C.rectus	0.85
Calprotectin + P.gingivalis + IL1beta + F.nucleatum	0.85
OPG + T.forsythia + IL4 + F.nucleatum	0.85
P.gingivalis + ICTP + IL1beta + F.nucleatum	0.85
T.forsythia + IL1beta + TNFa + F.nucleatum	0.85
T.denticola + IL6 + IL2	0.85
OPG + P.gingivalis + IL6 + F.nucleatum	0.85
OPG + T.forsythia + IL1beta + F.nucleatum	0.85
T.forsythia + IL4 + TNFa + F.nucleatum	0.85
T.forsythia + IL6 + ICTP	0.85
OPG + P.gingivalis + T.forsythia + IL1beta	0.85
T.denticola + IL1beta + IL4 + F.nucleatum	0.85
T.forsythia + IL6 + C.rectus	0.85
T.forsythia + IL13 + F.nucleatum	0.85
OPG + T.forsythia + TNFa + C.rectus	0.85
P.gingivalis + IL6 + IL1beta + F.nucleatum	0.85
P.gingivalis + IL6 + IL13 + C.rectus	0.85
T.forsythia + IL6 + IL10 + F.nucleatum	0.85
T.forsythia + IL6 + IL2 + F.nucleatum	0.85
Calprotectin + T.denticola	0.85
Calprotectin + OPG + P.gingivalis	0.85
T.forsythia + IL13 + TNFa + C.rectus	0.85
T.denticola + IL6 + TNFa	0.85
OPG + T.forsythia + IL2 + F.nucleatum	0.85
OPG + T.forsythia + IL2 + C.rectus	0.85
P.gingivalis + IL6 + IL10 + F.nucleatum	0.85
T.forsythia + IL13 + IL4 + C.rectus	0.85
Calprotectin + T.denticola + IL1beta	0.85
OPG + T.denticola + TNFa	0.85
OPG + P.gingivalis + ICTP + F.nucleatum	0.85
Calprotectin + T.forsythia + TNFa	0.85
T.forsythia + IL2 + IL13 + C.rectus	0.85
T.forsythia + IL2 + TNFa + F.nucleatum	0.85
T.denticola + IL10 + IL2 + F.nucleatum	0.85
T.forsythia + IL13 + C.rectus	0.85
T.denticola + IL6 + IL1beta	0.85
T.denticola + IL4 + TNFa + F.nucleatum	0.85
T.forsythia + IL6 + F.nucleatum	0.85
T.denticola + IL6 + IL4	0.85
P.gingivalis + T.forsythia + IL10 + IL4	0.85
T.denticola + IL4 + F.nucleatum	0.85
OPG + T.forsythia + IL10 + F.nucleatum	0.85
P.gingivalis + IL6 + IL4 + F.nucleatum	0.85
T.forsythia + IL1beta + IL13 + C.rectus	0.85

<u>Signature</u>	<u>AUC</u>
OPG + T.forsythia + F.nucleatum	0.85
T.forsythia + TNFa + F.nucleatum	0.85
Calprotectin + T.forsythia + IL1beta	0.85
P.gingivalis + IL6 + IL2 + F.nucleatum	0.85
P.gingivalis + ICTP + IL4 + F.nucleatum	0.85
OPG + T.denticola + IL2	0.85
P.gingivalis + ICTP + IL2 + F.nucleatum	0.85
P.gingivalis + IL6 + F.nucleatum	0.85
T.denticola + IL1beta + F.nucleatum	0.85
OPG + T.forsythia + IL10 + C.rectus	0.85
OPG + T.forsythia + C.rectus	0.85
P.gingivalis + T.forsythia + IL2 + IL4	0.85
T.forsythia + IL1beta + IL10 + F.nucleatum	0.85
T.forsythia + IL1beta + IL2 + F.nucleatum	0.85
T.denticola + TNFa + F.nucleatum	0.85
OPG + T.denticola + IL1beta	0.85
OPG + P.gingivalis + IL6 + C.rectus	0.85
T.forsythia + ICTP + TNFa	0.85
T.denticola + IL2 + IL13	0.85
P.gingivalis + T.forsythia + IL1beta + IL10	0.85
T.forsythia + IL1beta + IL4 + F.nucleatum	0.85
T.denticola + F.nucleatum	0.85
T.denticola + IL6 + IL10	0.85
T.denticola + IL1beta + IL13	0.85
T.forsythia + IL2 + IL4 + F.nucleatum	0.85
T.denticola + IL6	0.85
T.forsythia + IL1beta + F.nucleatum	0.85
Calprotectin + P.gingivalis + IL10	0.85
OPG + T.forsythia + ICTP	0.85
P.gingivalis + T.forsythia + IL10 + TNFa	0.85
OPG + T.denticola	0.85
Calprotectin + T.forsythia + IL4	0.85
OPG + T.denticola + IL4	0.85
T.forsythia + IL10 + IL13	0.85
T.forsythia + IL2 + IL4 + C.rectus	0.85
T.denticola + IL1beta + TNFa + F.nucleatum	0.85
P.gingivalis + T.forsythia + IL2	0.85
T.forsythia + IL1beta + IL4 + C.rectus	0.85
T.forsythia + IL2 + TNFa + C.rectus	0.85
T.denticola + IL13 + IL4	0.85
Calprotectin + T.forsythia + IL10	0.85
T.forsythia + IL1beta + IL10 + C.rectus	0.85
T.forsythia + IL1beta + IL2 + C.rectus	0.85
T.forsythia + IL1beta + TNFa + C.rectus	0.85
T.forsythia + IL10 + IL4 + F.nucleatum	0.85

<u>Signature</u>	<u>AUC</u>
Calprotectin + P.gingivalis + IL2	0.84
P.gingivalis + IL6 + IL13	0.84
P.gingivalis + T.forsythia + IL2 + TNFa	0.84
P.gingivalis + IL6 + TNFa + C.rectus	0.84
T.forsythia + IL1beta + C.rectus	0.84
P.gingivalis + IL6 + IL4 + C.rectus	0.84
Calprotectin + T.forsythia	0.84
P.gingivalis + ICTP + F.nucleatum	0.84
T.denticola + IL10 + IL2	0.84
P.gingivalis + ICTP + TNFa + F.nucleatum	0.84
T.forsythia + IL4 + F.nucleatum	0.84
MMP8 + Calprotectin + P.intermedia + C.rectus	0.84
P.gingivalis + IL6 + IL2 + C.rectus	0.84
T.forsythia + TNFa + C.rectus	0.84
OPG + T.forsythia + IL13	0.84
P.gingivalis + IL6 + IL1beta + C.rectus	0.84
P.gingivalis + T.forsythia + IL4	0.84
P.gingivalis + IL6 + C.rectus	0.84
T.forsythia + ICTP + IL1beta	0.84
T.denticola + IL2 + TNFa	0.84
OPG + P.gingivalis + IL10 + F.nucleatum	0.84
P.gingivalis + ICTP + IL13 + F.nucleatum	0.84
T.forsythia + IL10 + IL4 + C.rectus	0.84
T.forsythia + IL10 + TNFa + C.rectus	0.84
T.forsythia + IL4 + TNFa + C.rectus	0.84
T.forsythia + IL4 + C.rectus	0.84
Calprotectin + T.forsythia + IL2	0.84
Calprotectin + P.gingivalis + IL13	0.84
T.denticola + IL10 + TNFa	0.84
T.denticola + IL13 + TNFa	0.84
P.gingivalis + ICTP + IL10 + C.rectus	0.84
T.forsythia + IL2 + F.nucleatum	0.84
Calprotectin + P.gingivalis + IL1beta	0.84
P.gingivalis + ICTP + IL1beta + C.rectus	0.84
P.gingivalis + ICTP + IL4 + C.rectus	0.84
Calprotectin + P.gingivalis + IL4	0.84
T.forsythia + IL13 + TNFa	0.84
P.gingivalis + T.forsythia + IL1beta + IL4	0.84
P.gingivalis + ICTP + IL2 + C.rectus	0.84
T.denticola + IL13	0.84
T.forsythia + ICTP + IL4	0.84
P.gingivalis + ICTP + IL10	0.84
T.forsythia + IL13 + IL4	0.84
P.gingivalis + T.forsythia + IL4 + TNFa	0.84
P.gingivalis + ICTP + TNFa + C.rectus	0.84

<u>Signature</u>	<u>AUC</u>
T.forsythia + IL10 + IL2 + F.nucleatum	0.84
P.gingivalis + T.forsythia + TNFa	0.84
T.forsythia + IL2 + IL13	0.84
Calprotectin + MMP9 + P.intermedia + C.rectus	0.84
P.gingivalis + IL6 + IL10 + C.rectus	0.84
T.forsythia + IL10 + F.nucleatum	0.84
OPG + P.gingivalis + IL6	0.84
T.forsythia + ICTP + IL10	0.84
P.gingivalis + T.forsythia	0.84
T.denticola + IL1beta + IL10	0.84
OPG + P.gingivalis + ICTP + C.rectus	0.84
P.gingivalis + T.forsythia + IL1beta + TNFa	0.84
T.forsythia + F.nucleatum	0.84
T.forsythia + IL10 + C.rectus	0.84
T.denticola + IL10 + IL4	0.84
Calprotectin + P.gingivalis + TNFa	0.84
Calprotectin + MMP9 + P.intermedia + F.nucleatum	0.84
P.gingivalis + T.forsythia + IL1beta + IL2	0.84
T.denticola + IL10	0.84
T.forsythia + IL6 + TNFa	0.84
MMP8 + Calprotectin + P.intermedia + F.nucleatum	0.84
T.forsythia + ICTP + IL2	0.84
T.forsythia + IL10 + IL2 + C.rectus	0.84
P.gingivalis + ICTP + C.rectus	0.84
T.forsythia + IL2 + C.rectus	0.84
T.forsythia + IL1beta + IL13	0.84
T.denticola + IL2 + IL4	0.84
P.gingivalis + ICTP + IL13 + C.rectus	0.84
P.gingivalis + IL10 + TNFa + F.nucleatum	0.84
P.gingivalis + T.forsythia + IL1beta	0.84
T.denticola + IL1beta + IL2	0.84
T.forsythia + C.rectus	0.84
T.forsythia + ICTP	0.84
MMP8 + ICTP + P.intermedia + F.nucleatum	0.84
MMP8 + ICTP + P.intermedia + C.rectus	0.84
OPG + P.gingivalis + IL4 + F.nucleatum	0.84
P.gingivalis + IL10 + IL2 + F.nucleatum	0.84
T.forsythia + IL13	0.84
P.gingivalis + IL10 + F.nucleatum	0.84
Calprotectin + P.gingivalis	0.84
T.denticola + IL2	0.84
OPG + T.forsythia + IL6	0.84
P.gingivalis + ICTP + IL1beta	0.84
P.gingivalis + IL1beta + IL10 + F.nucleatum	0.84
P.gingivalis + IL10 + IL4 + F.nucleatum	0.84

<u>Signature</u>	<u>AUC</u>
P.gingivalis + IL6 + TNFa	0.84
T.forsythia + IL6 + IL1beta	0.83
P.gingivalis + IL6 + IL2	0.83
P.gingivalis + ICTP + IL4	0.83
OPG + P.gingivalis + IL1beta + F.nucleatum	0.83
P.gingivalis + ICTP + IL2	0.83
MMP8 + TNFa + P.intermedia + F.nucleatum	0.83
OPG + P.gingivalis + IL2 + F.nucleatum	0.83
P.gingivalis + IL13 + IL4 + F.nucleatum	0.83
MMP8 + Calprotectin + P.intermedia	0.83
OPG + P.gingivalis + TNFa + F.nucleatum	0.83
T.forsythia + IL6 + IL10	0.83
OPG + P.gingivalis + ICTP	0.83
P.gingivalis + IL6 + IL10	0.83
T.forsythia + IL6 + IL4	0.83
P.gingivalis + IL6 + IL1beta	0.83
T.denticola + IL4 + TNFa	0.83
OPG + P.gingivalis + F.nucleatum	0.83
P.gingivalis + IL6	0.83
OPG + T.forsythia + TNFa	0.83
P.gingivalis + IL1beta + IL4 + F.nucleatum	0.83
P.gingivalis + IL2 + IL13 + F.nucleatum	0.83
P.gingivalis + IL2 + IL4 + F.nucleatum	0.83
OPG + P.gingivalis + IL13 + F.nucleatum	0.83
Calprotectin + MMP9 + P.intermedia	0.83
P.gingivalis + IL2 + TNFa + F.nucleatum	0.83
P.gingivalis + IL1beta + IL2 + F.nucleatum	0.83
P.gingivalis + IL4 + F.nucleatum	0.83
P.gingivalis + IL6 + IL4	0.83
P.gingivalis + IL2 + F.nucleatum	0.83
MMP8 + ICTP + P.intermedia	0.83
P.gingivalis + ICTP + IL13	0.83
P.gingivalis + IL4 + TNFa + F.nucleatum	0.83
P.gingivalis + ICTP + TNFa	0.83
P.gingivalis + IL13 + TNFa + F.nucleatum	0.83
P.gingivalis + IL1beta + F.nucleatum	0.83
P.gingivalis + IL1beta + IL13 + F.nucleatum	0.83
P.gingivalis + IL1beta + TNFa + F.nucleatum	0.83
T.forsythia + IL6 + IL2	0.83
T.denticola + IL1beta + IL4	0.83
P.gingivalis + F.nucleatum + C.rectus	0.83
P.gingivalis + ICTP	0.83
MMP8 + TNFa + P.intermedia	0.83
OPG + T.forsythia + IL1beta	0.83
OPG + T.forsythia + IL4	0.83

<u>Signature</u>	<u>AUC</u>
MMP8 + IL1beta + P.intermedia + F.nucleatum	0.83
P.gingivalis + TNFa + F.nucleatum	0.83
T.denticola + IL4	0.83
T.denticola + IL1beta + TNFa	0.83
T.denticola + TNFa	0.83
MMP8 + TNFa + P.intermedia + C.rectus	0.83
P.gingivalis + IL10 + IL13 + C.rectus	0.83
MMP9 + TNFa + P.intermedia + C.rectus	0.83
P.gingivalis + IL1beta + IL10 + C.rectus	0.83
P.gingivalis + IL13 + F.nucleatum	0.83
OPG + P.gingivalis + IL10 + C.rectus	0.83
MMP8 + IL1beta + P.intermedia + C.rectus	0.82
T.forsythia + IL6	0.82
P.gingivalis + IL1beta + IL2 + C.rectus	0.82
OPG + T.forsythia + IL10	0.82
P.gingivalis + F.nucleatum	0.82
T.denticola + IL1beta	0.82
OPG + T.forsythia + IL2	0.82
P.gingivalis + IL10 + IL2 + C.rectus	0.82
P.gingivalis + IL2 + IL13 + C.rectus	0.82
T.denticola	0.82
MMP9 + TNFa + P.intermedia	0.82
T.forsythia + IL2 + TNFa	0.82
Calprotectin + TNFa + P.intermedia + F.nucleatum	0.82
MMP9 + TNFa + P.intermedia + F.nucleatum	0.82
OPG + P.gingivalis + IL13 + C.rectus	0.82
OPG + T.forsythia	0.82
MMP8 + IL10 + P.intermedia + F.nucleatum	0.82
MMP8 + IL6 + P.intermedia + F.nucleatum	0.82
OPG + P.gingivalis + IL1beta + C.rectus	0.82
P.gingivalis + IL13 + IL4 + C.rectus	0.82
Calprotectin + ICTP + P.intermedia + F.nucleatum	0.82
OPG + P.gingivalis + C.rectus	0.82
T.forsythia + IL4 + TNFa	0.82
MMP9 + IL1beta + P.intermedia + C.rectus	0.82
T.forsythia + IL1beta + TNFa	0.82
MMP9 + ICTP + P.intermedia + C.rectus	0.82
OPG + P.gingivalis + IL2 + C.rectus	0.82
OPG + P.gingivalis + TNFa + C.rectus	0.82
MMP8 + OPG + P.intermedia + F.nucleatum	0.82
OPG + P.gingivalis + IL4 + C.rectus	0.82
MMP8 + P.intermedia + F.nucleatum	0.82
MMP8 + IL13 + P.intermedia + C.rectus	0.82
P.gingivalis + IL10 + IL13	0.82
MMP8 + IL13 + P.intermedia + F.nucleatum	0.82

<u>Signature</u>	<u>AUC</u>
MMP9 + ICTP + P.intermedia + F.nucleatum	0.82
P.gingivalis + IL2 + IL4 + C.rectus	0.82
P.gingivalis + IL10 + TNFa + C.rectus	0.82
Calprotectin + ICTP + P.intermedia + C.rectus	0.82
T.forsythia + TNFa	0.82
MMP8 + IL1beta + P.intermedia	0.82
OPG + P.gingivalis + IL10	0.82
MMP8 + IL2 + P.intermedia + F.nucleatum	0.82
P.gingivalis + IL10 + IL4 + C.rectus	0.82
MMP8 + MMP9 + P.intermedia + C.rectus	0.82
MMP8 + IL4 + P.intermedia + F.nucleatum	0.82
P.gingivalis + IL10 + C.rectus	0.82
T.forsythia + IL10 + TNFa	0.82
MMP9 + IL1beta + P.intermedia + F.nucleatum	0.82
P.gingivalis + IL13 + TNFa + C.rectus	0.82
P.gingivalis + IL2 + C.rectus	0.82
MMP8 + MMP9 + P.intermedia + F.nucleatum	0.82
MMP8 + OPG + P.intermedia + C.rectus	0.82
MMP8 + IL10 + P.intermedia + C.rectus	0.82
MMP9 + IL2 + P.intermedia + C.rectus	0.82
P.gingivalis + IL2 + TNFa + C.rectus	0.82
Calprotectin + MMP9 + F.nucleatum + C.rectus	0.81
MMP8 + IL6 + P.intermedia	0.81
OPG + P.gingivalis + IL1beta	0.81
MMP8 + IL2 + P.intermedia + C.rectus	0.81
MMP8 + OPG + P.intermedia	0.81
OPG + P.gingivalis + IL4	0.81
MMP8 + IL6 + P.intermedia + C.rectus	0.81
P.gingivalis + IL1beta + IL4 + C.rectus	0.81
MMP8 + P.intermedia + C.rectus	0.81
P.gingivalis + IL4 + C.rectus	0.81
P.gingivalis + IL10 + IL2	0.81
MMP9 + IL4 + P.intermedia + F.nucleatum	0.81
P.gingivalis + IL1beta + TNFa + C.rectus	0.81
P.gingivalis + IL4 + TNFa + C.rectus	0.81
T.forsythia + IL1beta + IL4	0.81
P.gingivalis + TNFa + C.rectus	0.81
OPG + P.gingivalis + IL2	0.81
T.forsythia + IL2 + IL4	0.81
MMP8 + IL4 + P.intermedia + C.rectus	0.81
Calprotectin + IL2 + P.intermedia + F.nucleatum	0.81
T.forsythia + IL1beta	0.81
P.gingivalis + IL1beta + C.rectus	0.81
T.forsythia + IL1beta + IL10	0.81
MMP9 + ICTP + P.intermedia	0.81

<u>Signature</u>	<u>AUC</u>
P.gingivalis + IL1beta + IL10	0.81
P.gingivalis + IL2 + IL13	0.81
Calprotectin + IL10 + P.intermedia + F.nucleatum	0.81
P.gingivalis + IL13 + C.rectus	0.81
Calprotectin + OPG + P.intermedia + F.nucleatum	0.81
T.forsythia + IL1beta + IL2	0.81
Calprotectin + TNFa + P.intermedia + C.rectus	0.81
Calprotectin + IL13 + P.intermedia + F.nucleatum	0.81
OPG + P.gingivalis + TNFa	0.81
MMP9 + IL2 + P.intermedia + F.nucleatum	0.81
P.gingivalis + IL1beta + IL13 + C.rectus	0.81
MMP8 + MMP9 + P.intermedia	0.81
P.gingivalis + IL1beta + IL2	0.81
Calprotectin + IL6 + P.intermedia + F.nucleatum	0.81
MMP9 + IL6 + P.intermedia + F.nucleatum	0.81
Calprotectin + P.intermedia + F.nucleatum	0.81
P.gingivalis + IL10 + IL4	0.81
T.forsythia + IL10 + IL4	0.81
Calprotectin + IL1beta + P.intermedia + F.nucleatum	0.81
Calprotectin + IL4 + P.intermedia + F.nucleatum	0.81
MMP9 + IL6 + P.intermedia + C.rectus	0.81
MMP9 + P.intermedia + F.nucleatum	0.81
Calprotectin + OPG + P.intermedia + C.rectus	0.81
OPG + P.gingivalis + IL13	0.81
MMP9 + IL13 + P.intermedia + C.rectus	0.81
P.gingivalis + C.rectus	0.81
MMP8 + IL13 + P.intermedia	0.81
P.gingivalis + IL10 + TNFa	0.81
P.gingivalis + IL13 + TNFa	0.81
P.gingivalis + IL13 + IL4	0.81
MMP9 + OPG + P.intermedia + C.rectus	0.81
T.forsythia + IL4	0.81
P.gingivalis + IL10	0.81
MMP8 + IL4 + P.intermedia	0.81
MMP9 + IL10 + P.intermedia + C.rectus	0.81
Calprotectin + IL10 + P.intermedia + C.rectus	0.81
Calprotectin + IL2 + P.intermedia + C.rectus	0.80
OPG + P.gingivalis	0.80
MMP9 + P.intermedia + C.rectus	0.80
MMP8 + IL10 + P.intermedia	0.80
P.gingivalis + IL2 + IL4	0.80
P.gingivalis + IL2 + TNFa	0.80
T.forsythia + IL10 + IL2	0.80
MMP9 + IL13 + P.intermedia + F.nucleatum	0.80
MMP8 + P.intermedia	0.80

<u>Signature</u>	<u>AUC</u>
Calprotectin + IL6 + P.intermedia + C.rectus	0.80
Calprotectin + IL4 + P.intermedia + C.rectus	0.80
MMP9 + OPG + P.intermedia + F.nucleatum	0.80
MMP8 + IL2 + P.intermedia	0.80
T.forsythia + IL10	0.80
IL4 + TNFa + P.intermedia + F.nucleatum	0.80
P.gingivalis + IL2	0.80
MMP9 + IL1beta + P.intermedia	0.80
MMP8 + Calprotectin + F.nucleatum + C.rectus	0.80
P.gingivalis + IL1beta + IL4	0.80
Calprotectin + P.intermedia + C.rectus	0.80
MMP9 + IL10 + P.intermedia + F.nucleatum	0.80
Calprotectin + TNFa + P.intermedia	0.80
MMP9 + IL2 + P.intermedia	0.80
Calprotectin + IL1beta + P.intermedia + C.rectus	0.80
P.gingivalis + IL1beta + IL13	0.80
Calprotectin + IL13 + P.intermedia + C.rectus	0.80
MMP9 + IL4 + P.intermedia + C.rectus	0.80
MMP9 + IL6 + P.intermedia	0.80
T.forsythia + IL2	0.80
Calprotectin + MMP9 + C.rectus	0.80
P.gingivalis + IL1beta	0.80
P.gingivalis + IL1beta + TNFa	0.80
MMP9 + OPG + P.intermedia	0.80
P.gingivalis + IL4 + TNFa	0.80
T.forsythia	0.80
P.gingivalis + IL4	0.80
Calprotectin + ICTP + P.intermedia	0.80

Table 3. Biomarker combinations resulting in an AUC (probability) value greater than 90%

<u>Signature</u>	<u>AUC</u>
MMP8 + T.denticola + ICTP + C.rectus	0.95
MMP8 + T.denticola + ICTP + P.intermedia	0.95
MMP9 + T.denticola + ICTP + C.rectus	0.94
Calprotectin + T.denticola + ICTP + C.rectus	0.94
T.denticola + IL6 + ICTP + C.rectus	0.94
MMP8 + T.forsythia + T.denticola + ICTP	0.94
MMP9 + T.denticola + ICTP + P.intermedia	0.94
MMP8 + P.gingivalis + T.denticola + ICTP	0.93
MMP8 + T.denticola + IL1beta + P.intermedia	0.93
MMP9 + T.forsythia + T.denticola + ICTP	0.93
MMP8 + Calprotectin + P.gingivalis + P.intermedia	0.93

<u>Signature</u>	<u>AUC</u>
Calprotectin + MMP9 + T.denticola + C.rectus	0.93
T.denticola + ICTP + IL10 + C.rectus	0.93
T.forsythia + T.denticola + ICTP + IL13	0.93
MMP8 + T.denticola + TNFa + P.intermedia	0.93
MMP8 + Calprotectin + T.denticola + P.intermedia	0.93
MMP9 + P.gingivalis + T.denticola + ICTP	0.93
Calprotectin + MMP9 + P.gingivalis + P.intermedia	0.93
Calprotectin + T.denticola + ICTP + P.intermedia	0.93
T.denticola + ICTP + TNFa + P.intermedia	0.93
MMP8 + T.denticola + ICTP + F.nucleatum	0.93
MMP8 + OPG + T.denticola + P.intermedia	0.92
MMP8 + T.denticola + IL13 + P.intermedia	0.92
T.denticola + ICTP + IL13 + P.intermedia	0.92
T.forsythia + T.denticola + IL6 + ICTP	0.92
T.denticola + ICTP + IL2 + C.rectus	0.92
MMP8 + T.denticola + ICTP	0.92
MMP8 + T.denticola + IL4 + P.intermedia	0.92
T.denticola + IL6 + ICTP + P.intermedia	0.92
MMP9 + T.denticola + TNFa + P.intermedia	0.92
T.denticola + ICTP + IL1beta + C.rectus	0.92
Calprotectin + MMP9 + T.denticola + P.intermedia	0.92
T.denticola + ICTP + IL1beta + P.intermedia	0.92
OPG + T.denticola + ICTP + C.rectus	0.92
T.denticola + ICTP + IL4 + C.rectus	0.92
T.denticola + ICTP + C.rectus	0.92
MMP8 + P.gingivalis + ICTP + P.intermedia	0.92
MMP8 + T.forsythia + IL1beta + P.intermedia	0.92
T.denticola + ICTP + IL4 + P.intermedia	0.92
T.denticola + ICTP + IL13 + C.rectus	0.92
MMP9 + T.denticola + IL1beta + P.intermedia	0.92
OPG + T.denticola + ICTP + P.intermedia	0.92
OPG + T.forsythia + T.denticola + ICTP	0.92
MMP8 + Calprotectin + T.denticola + C.rectus	0.92
MMP8 + OPG + T.denticola + C.rectus	0.92
MMP9 + T.denticola + IL13 + P.intermedia	0.92
T.denticola + ICTP + IL10 + P.intermedia	0.92
T.denticola + ICTP + TNFa + C.rectus	0.92
MMP8 + Calprotectin + T.forsythia + P.intermedia	0.92
MMP8 + T.denticola + IL6 + P.intermedia	0.92
MMP9 + T.denticola + IL1beta + C.rectus	0.92
P.gingivalis + T.denticola + IL6 + ICTP	0.92
MMP8 + T.denticola + IL1beta + C.rectus	0.92
T.denticola + ICTP + P.intermedia	0.92
T.denticola + ICTP + IL2 + P.intermedia	0.92
MMP8 + T.denticola + P.intermedia	0.92

<u>Signature</u>	<u>AUC</u>
MMP8 + P.gingivalis + IL1beta + P.intermedia	0.92
MMP8 + T.forsythia + T.denticola + IL1beta	0.92
T.forsythia + T.denticola + ICTP + TNFa	0.92
MMP8 + T.forsythia + TNFa + P.intermedia	0.92
MMP9 + OPG + T.denticola + C.rectus	0.92
T.forsythia + T.denticola + ICTP + IL1beta	0.92
Calprotectin + T.forsythia + T.denticola + ICTP	0.92
MMP8 + MMP9 + T.denticola + P.intermedia	0.92
MMP8 + T.denticola + IL2 + P.intermedia	0.92
MMP9 + T.denticola + ICTP + F.nucleatum	0.92
Calprotectin + MMP9 + T.forsythia + P.intermedia	0.92
MMP9 + OPG + T.denticola + P.intermedia	0.92
MMP9 + T.denticola + IL4 + P.intermedia	0.92
MMP9 + T.denticola + ICTP	0.91
T.forsythia + T.denticola + ICTP + IL10	0.91
MMP8 + T.forsythia + ICTP + P.intermedia	0.91
T.forsythia + T.denticola + ICTP + IL4	0.91
MMP8 + P.gingivalis + TNFa + P.intermedia	0.91
Calprotectin + MMP9 + P.gingivalis + T.denticola	0.91
Calprotectin + OPG + T.denticola + C.rectus	0.91
T.forsythia + T.denticola + ICTP + IL2	0.91
MMP8 + T.denticola + IL10 + P.intermedia	0.91
MMP9 + T.forsythia + T.denticola + IL1beta	0.91
MMP8 + T.forsythia + IL13 + P.intermedia	0.91
Calprotectin + MMP9 + T.forsythia + T.denticola	0.91
Calprotectin + T.denticola + IL6 + C.rectus	0.91
MMP9 + T.denticola + TNFa + C.rectus	0.91
MMP8 + Calprotectin + T.forsythia + T.denticola	0.91
Calprotectin + T.denticola + IL13 + P.intermedia	0.91
MMP8 + MMP9 + T.denticola + C.rectus	0.91
MMP8 + OPG + T.forsythia + T.denticola	0.91
Calprotectin + T.denticola + TNFa + P.intermedia	0.91
T.forsythia + T.denticola + ICTP	0.91
MMP8 + P.gingivalis + T.denticola + IL1beta	0.91
MMP8 + T.forsythia + T.denticola + IL13	0.91
MMP9 + T.forsythia + T.denticola + IL13	0.91
MMP9 + T.forsythia + TNFa + P.intermedia	0.91
MMP9 + T.denticola + IL6 + C.rectus	0.91
OPG + P.gingivalis + T.denticola + ICTP	0.91
Calprotectin + OPG + T.denticola + P.intermedia	0.91
P.gingivalis + T.denticola + ICTP + IL10	0.91
MMP8 + P.gingivalis + IL13 + P.intermedia	0.91
MMP8 + P.gingivalis + IL4 + P.intermedia	0.91
MMP8 + T.denticola + IL4 + C.rectus	0.91
MMP8 + T.denticola + TNFa + C.rectus	0.91

<u>Signature</u>	<u>AUC</u>
MMP9 + OPG + T.forsythia + T.denticola	0.91
MMP9 + T.denticola + IL6 + P.intermedia	0.91
MMP9 + T.denticola + IL2 + P.intermedia	0.91
MMP9 + T.denticola + P.intermedia	0.91
MMP8 + Calprotectin + P.gingivalis + T.denticola	0.91
MMP9 + P.gingivalis + ICTP + P.intermedia	0.91
MMP9 + T.forsythia + T.denticola + TNFa	0.91
MMP8 + T.forsythia + IL4 + P.intermedia	0.91
MMP9 + P.gingivalis + T.denticola + IL13	0.91
MMP9 + T.denticola + IL4 + C.rectus	0.91
T.denticola + IL6 + ICTP + F.nucleatum	0.91
MMP8 + T.forsythia + T.denticola + TNFa	0.91
MMP8 + T.denticola + IL10 + C.rectus	0.91
Calprotectin + P.gingivalis + T.denticola + ICTP	0.91
Calprotectin + T.denticola + ICTP + F.nucleatum	0.91
Calprotectin + T.denticola + IL4 + P.intermedia	0.91
P.gingivalis + T.denticola + ICTP + IL13	0.91
MMP8 + P.gingivalis + T.denticola + IL13	0.91
Calprotectin + P.gingivalis + ICTP + P.intermedia	0.91
MMP9 + T.denticola + IL10 + C.rectus	0.91
MMP9 + P.gingivalis + IL1beta + P.intermedia	0.91
MMP8 + OPG + P.gingivalis + T.denticola	0.91
MMP8 + T.denticola + IL6 + C.rectus	0.91
MMP9 + OPG + P.gingivalis + T.denticola	0.91
MMP9 + P.gingivalis + T.denticola + IL1beta	0.91
MMP9 + T.forsythia + IL13 + P.intermedia	0.91
MMP8 + T.denticola + IL13 + C.rectus	0.91
Calprotectin + T.denticola + IL10 + C.rectus	0.91
MMP8 + T.denticola + C.rectus	0.91
MMP8 + OPG + T.forsythia + P.intermedia	0.91
MMP8 + T.forsythia + T.denticola + IL4	0.91
MMP9 + T.forsythia + T.denticola + IL4	0.91
MMP9 + T.denticola + IL2 + C.rectus	0.91
MMP9 + T.denticola + IL13 + C.rectus	0.91
OPG + T.denticola + IL13 + P.intermedia	0.91
MMP8 + OPG + P.gingivalis + P.intermedia	0.91
MMP9 + T.forsythia + IL1beta + P.intermedia	0.91
MMP9 + T.denticola + IL10 + P.intermedia	0.91
MMP8 + T.denticola + IL2 + C.rectus	0.91
Calprotectin + T.forsythia + T.denticola + IL13	0.91
MMP9 + T.denticola + C.rectus	0.91
P.gingivalis + T.denticola + ICTP + TNFa	0.91
MMP8 + P.gingivalis + T.denticola + IL4	0.91
MMP8 + P.gingivalis + IL2 + P.intermedia	0.91
Calprotectin + T.denticola + IL6 + P.intermedia	0.91

<u>Signature</u>	<u>AUC</u>
Calprotectin + T.denticola + IL1beta + P.intermedia	0.91
MMP9 + P.gingivalis + T.denticola + IL4	0.91
P.gingivalis + T.denticola + ICTP + IL2	0.91
P.gingivalis + T.denticola + ICTP + IL4	0.91
T.denticola + IL2 + IL13 + P.intermedia	0.91
OPG + T.denticola + ICTP + F.nucleatum	0.90
T.denticola + ICTP + IL10 + F.nucleatum	0.90
T.denticola + IL1beta + IL13 + P.intermedia	0.90
T.denticola + IL6 + ICTP	0.90
MMP8 + T.forsythia + IL10 + P.intermedia	0.90
T.denticola + ICTP + IL2 + F.nucleatum	0.90
MMP8 + T.forsythia + IL6 + P.intermedia	0.90
MMP9 + P.gingivalis + T.denticola + TNFa	0.90
MMP9 + P.gingivalis + IL13 + P.intermedia	0.90
MMP9 + T.forsythia + ICTP + P.intermedia	0.90
T.forsythia + T.denticola + P.intermedia	0.90
MMP8 + P.gingivalis + P.intermedia	0.90
MMP8 + MMP9 + P.gingivalis + T.denticola	0.90
Calprotectin + T.denticola + P.intermedia	0.90
MMP8 + P.gingivalis + IL6 + P.intermedia	0.90
Calprotectin + T.forsythia + ICTP + P.intermedia	0.90
Calprotectin + T.forsythia + IL13 + P.intermedia	0.90
MMP9 + P.gingivalis + IL4 + P.intermedia	0.90
MMP9 + P.gingivalis + TNFa + P.intermedia	0.90
T.denticola + IL10 + IL13 + P.intermedia	0.90
P.gingivalis + T.denticola + ICTP	0.90
MMP8 + P.gingivalis + T.forsythia + ICTP	0.90
MMP8 + P.gingivalis + T.denticola + TNFa	0.90
Calprotectin + MMP9 + T.forsythia + C.rectus	0.90
Calprotectin + T.denticola + IL10 + P.intermedia	0.90
P.gingivalis + T.denticola + P.intermedia	0.90
MMP8 + P.gingivalis + T.denticola + IL2	0.90
MMP8 + MMP9 + T.forsythia + T.denticola	0.90
Calprotectin + MMP9 + P.gingivalis + T.forsythia	0.90
MMP9 + P.gingivalis + T.forsythia + ICTP	0.90
P.gingivalis + T.denticola + ICTP + IL1beta	0.90
T.denticola + IL6 + IL13 + P.intermedia	0.90
T.denticola + ICTP + IL13 + F.nucleatum	0.90
MMP8 + Calprotectin + T.denticola + F.nucleatum	0.90
MMP8 + P.gingivalis + IL10 + P.intermedia	0.90
MMP8 + Calprotectin + P.gingivalis + T.forsythia	0.90
MMP8 + OPG + T.denticola + F.nucleatum	0.90
MMP8 + T.forsythia + T.denticola + IL2	0.90
Calprotectin + T.denticola + IL2 + P.intermedia	0.90
Calprotectin + T.denticola + IL13 + C.rectus	0.90

<u>Signature</u>	<u>AUC</u>
MMP9 + T.forsythia + IL4 + P.intermedia	0.90
T.denticola + IL13 + IL4 + P.intermedia	0.90
MMP8 + T.forsythia + IL2 + P.intermedia	0.90
Calprotectin + MMP9 + T.denticola + F.nucleatum	0.90
T.denticola + ICTP + TNFa + F.nucleatum	0.90
T.denticola + IL13 + TNFa + P.intermedia	0.90
Calprotectin + MMP9 + P.gingivalis + C.rectus	0.90
MMP9 + T.forsythia + T.denticola + IL10	0.90
MMP9 + T.forsythia + IL2 + P.intermedia	0.90
MMP8 + MMP9 + P.gingivalis + P.intermedia	0.90
Calprotectin + T.denticola + IL2 + C.rectus	0.90
Calprotectin + T.denticola + C.rectus	0.90
T.denticola + IL13 + P.intermedia	0.90
Calprotectin + T.denticola + ICTP	0.90
Calprotectin + T.denticola + TNFa + C.rectus	0.90
OPG + T.denticola + IL4 + P.intermedia	0.90
T.denticola + ICTP + IL4 + F.nucleatum	0.90
T.denticola + ICTP + IL1beta + F.nucleatum	0.90
MMP8 + T.forsythia + T.denticola	0.90
MMP8 + T.forsythia + P.intermedia	0.90
MMP9 + T.forsythia + T.denticola	0.90
MMP8 + P.gingivalis + T.denticola + IL10	0.90
Calprotectin + OPG + P.gingivalis + P.intermedia	0.90
Calprotectin + P.gingivalis + TNFa + P.intermedia	0.90
MMP9 + T.forsythia + T.denticola + IL6	0.90
MMP9 + T.forsythia + IL10 + P.intermedia	0.90
T.denticola + ICTP + F.nucleatum	0.90
Calprotectin + T.denticola + IL4 + C.rectus	0.90
OPG + T.denticola + TNFa + P.intermedia	0.90
MMP8 + T.forsythia + T.denticola + IL6	0.90
MMP8 + T.forsythia + T.denticola + IL10	0.90
MMP8 + T.forsythia + ICTP + C.rectus	0.90
MMP8 + T.denticola + IL1beta + F.nucleatum	0.90
Calprotectin + P.gingivalis + IL4 + P.intermedia	0.90
MMP9 + P.gingivalis + T.denticola + IL6	0.90
Calprotectin + P.gingivalis + IL13 + P.intermedia	0.90
MMP9 + OPG + P.gingivalis + P.intermedia	0.90
MMP9 + P.gingivalis + IL2 + P.intermedia	0.90
T.denticola + IL6 + TNFa + P.intermedia	0.90
T.denticola + IL2 + TNFa + P.intermedia	0.90
T.denticola + P.intermedia + C.rectus	0.90
MMP9 + OPG + T.denticola + F.nucleatum	0.90
OPG + T.denticola + IL6 + P.intermedia	0.90
OPG + T.denticola + IL1beta + P.intermedia	0.90
MMP8 + P.gingivalis + T.denticola	0.90

<u>Signature</u>	<u>AUC</u>
MMP9 + P.gingivalis + T.denticola	0.90
Calprotectin + OPG + T.forsythia + P.intermedia	0.90
Calprotectin + T.denticola + IL1beta + C.rectus	0.90
MMP9 + OPG + T.forsythia + P.intermedia	0.90
MMP9 + P.gingivalis + T.forsythia + IL13	0.90
T.denticola + IL10 + TNFa + P.intermedia	0.90
Calprotectin + OPG + T.forsythia + C.rectus	0.90
Calprotectin + P.gingivalis + IL10 + P.intermedia	0.90
Calprotectin + T.forsythia + TNFa + P.intermedia	0.90
T.denticola + IL6 + IL4 + P.intermedia	0.90
T.denticola + IL2 + IL4 + P.intermedia	0.90
MMP9 + P.gingivalis + T.denticola + IL2	0.90
MMP9 + T.denticola + IL1beta + F.nucleatum	0.90
T.forsythia + T.denticola + IL6 + IL13	0.90
Calprotectin + P.gingivalis + IL1beta + P.intermedia	0.90
MMP9 + P.gingivalis + T.forsythia + TNFa	0.90
T.denticola + IL6 + IL13 + C.rectus	0.90
Calprotectin + P.gingivalis + P.intermedia	0.90
MMP8 + P.gingivalis + T.forsythia + IL1beta	0.90
MMP8 + P.gingivalis + T.forsythia + TNFa	0.90
T.denticola + IL6 + IL2 + P.intermedia	0.90
T.denticola + IL10 + IL4 + P.intermedia	0.90
MMP9 + P.gingivalis + P.intermedia	0.90
T.denticola + ICTP + IL10	0.90
MMP8 + MMP9 + T.forsythia + P.intermedia	0.90
MMP9 + P.gingivalis + T.forsythia + IL1beta	0.90
MMP9 + T.forsythia + T.denticola + IL2	0.90
OPG + T.denticola + P.intermedia	0.90
MMP8 + P.gingivalis + T.forsythia + IL4	0.90
MMP8 + P.gingivalis + T.denticola + IL6	0.90
MMP8 + T.forsythia + IL1beta + C.rectus	0.90
Calprotectin + P.gingivalis + IL2 + P.intermedia	0.90
Calprotectin + T.forsythia + IL1beta + P.intermedia	0.90
MMP9 + P.gingivalis + T.forsythia + IL4	0.90
MMP9 + P.gingivalis + IL6 + P.intermedia	0.90
T.denticola + P.intermedia + F.nucleatum	0.90
MMP8 + OPG + T.denticola	0.90
MMP8 + P.gingivalis + T.forsythia + IL13	0.90
MMP8 + T.denticola + IL1beta	0.90
OPG + T.denticola + ICTP	0.90
Calprotectin + OPG + T.forsythia + T.denticola	0.90

[0060] In various aspects of methods of the invention, an AUC probability value that is at least about 60% or higher is indicative of oral disease. Indeed, the present invention

contemplates methods wherein an AUC value is calculable, and thereby prediction of a disease state at a probability that is greater than about 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 73%, 74%, 74%, 75%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more

[0061] According to methods of the invention, biomarker levels that are determined and used for the generation of ROC and AUC curves are protein levels. Methods for detection of protein levels in a sample are well known and routinely practiced in the art. For example the worker of ordinary skill in the art will appreciate that ELISA and western blotting methodologies are amenable to methods of the invention, as well as techniques such as a proximity-ligation strategy (3PLA) (Schallmeiner *et al.*, Nature Methods (2006) 4, 135 – 137), rolling circle amplification (RCA) -enhanced protein detection on antibody microarrays (Haab, *et al.*, Meth. Mol. Biol (2006) 328:15-29), high throughput microarray analyses as described, for example in Lee, *et al.*, Analyst, 2008, 133, 975-983 and other well known biomarker detection methods as described, for example, in Liszewski, Genetic Eng. Biotech. News., Mar 15 2006 (Vol. 26, No. 6), Pan, *et al.*, Molecular & Cellular Proteomics (2005) 4:182-190, Yan, *et al.*, J. Mass Spect. (2005) 40 (4): 444 – 451, and Archarya, *et al.*, J. Am. Chem. Soc.(2007) 129 (51):15824 -15829. Additional methods for protein detection well known in the art are described, for example, in Coligan, *et al.* (eds), Current Protocol in Protein Science, (John Wiley and Sons, last updated May 2008).

[0062] In other aspects, the levels are measured using DNA or RNA by methods well known and routinely practiced in the art. A comprehensive guide to methods for detection of polynucleotides is found, for example, in Ausubel, *et al.*, (eds) Current Protocols in Molecular Biology (John Wiley and Sons, last updated July 2008), and Sambrook, *et al.*, Molecular Cloning: A Laboratory Manual, (Cold Spring Harbor 2001).

[0063] Samples contemplated for use in carrying out the methods of the invention include a bodily fluid, tissue and organ. In various aspects, a sample can be saliva, a gingival tissue specimen, or gingival crevicular fluid (GCF). Methods for sample collection will be readily appreciated by those of ordinary skill in the art.

[0064] In still further aspects of the invention, a method for treating oral disease in an individual comprising the step of inhibiting activity of one or more biomarkers identified in methods of the invention to be indicative of oral disease in said individual is provided. In an embodiment of the methods, the biomarker activity is inhibited by an antibody, wherein said

antibody specifically binds to a biomarker and inhibits biomarker binding and/or prevents biomarker signaling and/or otherwise inhibits its activity. Inhibition of a detected biomarker is therefore effected by use of antibodies, peptides or small molecules against biomarkers that are capable of inhibiting the activity of said biomarkers. In still other aspects detected biomarkers are inhibited using known binding partners, or fragments of variants of known binding partners of the identified biomarkers, wherein the binding partner, or fragment or variant thereof specifically binds to and abrogate the function and/or activity of the biomarkers.

[0065] In other aspects of these methods, expression of the biomarker is inhibited and in a specific embodiment, expression of a biomarker or biomarkers is inhibited by inhibitory RNA. Because reduction in biomarker mRNA levels can lead to alteration in biomarker protein products of expression as well, such resultant alterations can also be measured. Production and use of inhibitory RNA, including, for example and without limitation, RNA interference, antisense RNA technology, shRNA, and/or ribozymes are described in Dykxhoo *et al.*, (2003), Nature Review, 4: 457-467, 2003; and Mittal, (2004) Nature Reviews, 5: 355-365.

[0066] Methods of reducing biomarker activity are contemplated by the invention through administration of a composition to an individual in need thereof. The administration is contemplated to be useful as either a therapeutic or prophylactic composition. In general, the compositions are used in order to treat oral disease by reducing or eliminating the biomarker expression or activity in gingival cells. "Reducing or eliminating" refers to a reduction or elimination of detectable amounts of the biomarker gene product by an amount in the range of at least about 10% to about 100%, or at least about 25% to 100%, at least about 50% to about 100%, and from about 75% to about 100%. Methods of the invention are therefore for inhibiting biomarker expression with a reduction of said biomarker transcription and/or biomarker protein translation, and/or biomarker protein activity by at least 10%, by at least 20%, by at least 25%, by at least 30%, by at least 40%, by at least 50%, by at least 60%, by at least 70%, by at least 75%, by at least 80%, by at least 85%, by at least 90%, by at least 95%, by at least 98%, by at least 99%, or by 100% in an individual. The result of the reduction in biomarker expression or activity will ultimately be a reduction in the AUC probability value as determined by the methods of the invention.

[0067] The present invention also provides a kit for carrying out the various methods of the invention, the kit comprising a sterile container for sample collection and one or more components selected from the group consisting of one or more reagents for performing the

assay, a calibration standard and a quality control sample. In another embodiment of the present invention, kits are provided which contain the necessary reagents to carry out the assays of the present invention. In one aspect, the invention provides a compartment kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising a probe or antibody that recognize a biomarker of the invention; and (b) one or more other containers comprising one or more of the following: wash reagents, reagents capable of detecting presence of a bound probe or antibody.

[0068] In detail, a compartment kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allows one to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are not cross contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the antibodies used in the assay, containers which contain wash reagents (such as phosphate buffered saline, Tris buffers, etc.), and containers which contain the reagents used to detect the bound antibody or probe. Types of detection reagents include labeled nucleic acid probes, labeled secondary antibodies, or in the alternative, if the primary antibody is labeled, the enzymatic, or antibody binding reagents which are capable of reacting with the labeled antibody. One skilled in the art will readily recognize that the disclosed probes and antibodies of the present invention can be readily incorporated into one of the established kit formats which are well known in the art.

[0069] As an additional aspect, the various kits contemplated by the invention contain suitable reagents for carrying out assays including but not limited to immunological assays (including enzyme-linked immunosorbent assays (ELISAs) and radioimmunoassay), polymerase chain reaction (PCR) analyses, quantitative PCR (qPCR) analyses, and buffers and other standard reagents (*e.g.*, primers) used in carrying out the assays, all of which are known to one of ordinary skill in the art. Preferably, the kit contains an insert that describes use of the kit.

[0070] While the present invention has been described in terms of various embodiments and examples, it is understood that variations and improvements will occur to those skilled in the art. Therefore, only such limitations as appear in the claims should be placed on the invention.

EXAMPLES

Example 1

[0071] Univariate Analyses: A total sample of 50 subjects, 9 who have moderate/severe periodontitis and 41 who do not were studied. Sixteen biomarkers were determined. There are missing values for some subjects in each of the biomarkers; 45 subjects have values for all of the biomarkers.

[0072] Table 4 (below) displays the following values for each biomarker: (A) the median and number of subjects evaluated for those without moderate/severe periodontitis; (B) the median and number of subjects evaluated for those with moderate/severe periodontitis; (C) the area-under-the ROC curve (AUC); and (D) the p-value corresponding to a test of a difference between the medians (Wilcoxon Rank Sum Test).

Table 4. Univariate summary statistics for each biomarker

<u>Median (N measured)</u>				
<u>Biomarker</u>	<u>Healthy/Mild</u> <u>Periodontitis</u>	<u>Moderate/Severe</u> <u>Periodontitis</u>	<u>AUC</u>	<u>p-value</u>
MMP-8	56.0 (41)	349.5 (9)	0.85	<0.001
MMP-9	231.8 (41)	859.7 (9)	0.76	0.015
IL-2	7.2 (41)	6.0* (8)	0.66	0.134
TNF- α	8.2 (41)	8.0* (8)	0.66	0.149
IL-5	20.0* (41)	20.0* (8)	0.65	0.089
Calprotectin	42.4 (41)	66.4 (9)	0.63	0.240
ICTP	0.7 (39)	0.9 (9)	0.63	0.236
IL-1 β	206.7 (41)	600.7 (8)	0.60	0.365
IL-10	123.5 (41)	60.0* (8)	0.60	0.353
Osteopontin	1.8 (41)	1.7 (7)	0.59	0.465
IL-6	6.0* (41)	78.7 (8)	0.56	0.543
IL-13	200* (41)	200.0* (8)	0.55	0.653
IL-4	42.8 (41)	19.5 (8)	0.55	0.681
Osteocalcin	17.1 (41)	18.4 (9)	0.54	7.43
Laminin	16.8 (41)	16.5 (9)	0.52	0.836
IFN- γ	60.0* (41)	60.0* (8)	0.51	0.958

* - Media equal to detection threshold

[0073] Table 5 (below) contains additional information on MMP-8 and MMP-9. The cut point determined for each biomarker was that value where the difference between sensitivity and specificity was as small as possible.

Table 5. Diagnostic Properties of MMP-8 and MMP-9

<u>Marker</u>	<u>Cut Pt.</u>	<u>Above Cut Pt.</u>	<u>Healthy/ Mild Periodontitis</u>	<u>Moderate/ Severe Periodontitis</u>	<u>p-value</u>	<u>Sens</u>	<u>Spec</u>	<u>PPV</u>	<u>NPV</u>
MMP-9	124.1	N	31	1	0.001	0/89	0.76	0.44	0.97
		Y	10	8					
MMP-9	370.1	N	26	3	0.200	0.67	0.63	0.29	0.90
		Y	15	6					

[0074] Multivariate Analyses - CART and Random Forest Methods: CART (Classification and Regression Trees) is a method that seeks to find the best biomarkers and the best cut-points of those biomarkers that discriminate between subjects with periodontitis and subjects without periodontitis. However, one limitation of CART is that no statistical significance (*i.e.*, p-value) of the model can be derived. Random Forests is a method that repeatedly resamples from the data and fits a CART model to each resampled set of data. An overall "importance score" is then derived for each biomarker that essentially reflects how often each biomarker appears in each CART model created from each resampled set of data. Thus, rather than a final "model", a list of biomarkers is generated that may prove useful for predicting moderate/severe periodontitis.

[0075] Table 6 (below) contains the importance scores of each biomarker, listed in descending order of importance score, based only upon the 45 subjects who had measurements for all 16 biomarkers. There is an obvious separation of MMP-8 from the others, and MMP-9 has a rather weak importance score. There are also indications that ICTP, calprotectin, and IL-1 β hold some promise, confirming the results in Table 4.

Table 6. Importance scores of 16 biomarkers in Random Forest models

<u>Biomaker</u>	<u>Importance Score</u>
MMP-8	1.83
ICTP	1.06
Calprotectin	1.05
IL-1 β	0.94
MMP-9	0.86
TNF- α	0.73
Osteopontin	0.69
Osteocalcin	0.54
IL-10	0.52
Laminin	0.50
IL-6	0.41
IL-4	0.41
IL-2	0.29
IL-13	0.25
IL-5	0.09
IFN- γ	0.05

[0076] Multivariate Analyses - Regression Methods: As an alternative to CART and Random Forests, multivariate logistic regression was used, simultaneously modeling the presence or absence of periodontitis in each subject on all of the corresponding biomarker values. The final model with a reduced subset of the biomarkers was then identified using stepwise regression techniques. The next step was to resample (bootstrap) from the original data and apply stepwise logistic regression techniques to identify the best subset of biomarkers based upon this resampled data set. This resampling and model-fitting process was repeated 1000 times, giving 1000 possible combinations of the best set of biomarkers to predict presence or absence of moderate/severe periodontitis.

[0077] Table 7 (below) contains the percentages that each biomarker appeared in the 1000 combinations; the biomarkers are sorted in descending order of percentage, based only upon the 45 subjects who had measurements for all 16 biomarkers. As in Table 4, MMP-8 and MMP-9 are likely candidate markers for moderate/severe periodontitis. However, Table 7 gives less support to calprotectin, IL-1 β , and ICTP.

Table 7. Percentage that each biomarker appeared in the 1000 combinations of 16 biomarkers in Random Forest models

<u>Biomaker</u>	<u>Percentage</u>
MMP-8	0.89
MMP-9	0.67
Osteopontin	0.41
Osteocalcin	0.37
IL-5	0.34
IL-2	0.32
IL-1 β	0.32
IL-6	0.30
IL-4	0.29
Calprotectin	0.28
TNF- α	0.25
ICTP	0.21
Laminin	0.19
IL-13	0.19
IL-10	0.13
IFN- γ	0.10

[0078] Using three different statistical approaches (Wilcoxon Rank Sum Test/AUC, CART/Random Forests, and Bootstrapped Stepwise Logistic Regression), the data indicate that MMP-8 is far and away the best biomarker for detecting moderate/severe periodontitis. There are modest indications that MMP-9, ICTP, calprotectin, and IL-1 β are also possible biomarkers for moderate/severe periodontitis.

[0079] CART was used again to find the combination of MMP-8, MMP-9, calprotectin, IL-1 β and ICTP that best discriminates between those with moderate/severe periodontitis (diseased) and those without moderate/severe periodontitis (healthy). The final model is shown in Figure 7; this model divides subjects into four groups (labeled as G1-G4). G3 is defined to be subjects with moderate/severe periodontitis and are those subjects with MMP-8 greater than 84.145 and ICTP between 0.705 and 1.37. Using this classification scheme, 4 of 6 subjects with moderate/severe periodontitis were correctly classified (sensitivity=0.67) and 38 of 39 subjects without moderate/severe periodontitis (specificity=0.97). Put another way, those classified as diseased in Figure 7 have 76 times the odds of moderate/severe

periodontitis as those classified as healthy in Figure 1 (odds ratio=76; 95% confidence interval =[6, 1036]).

Example 2

[0080] Another clinical study was approved by the University of Michigan Health Sciences Institutional Review Board (IRB) and registered with the NIH clinical trials database. Upon receiving written consent, a total of 100 human subjects aged 18 years and older were evaluated at the Michigan Center for Oral Health Research (MCOHR). All subjects possessed at least 20 teeth and had received no periodontal treatment or antibiotic therapy for medical or dental reasons three months prior to the investigation. In addition, the subjects did not previously undergo any long-term use of medications affecting periodontal status such as anti-inflammatory drugs before the study.

[0081] Subjects were enrolled into a low-risk disease population (N = 50) and a disease susceptible population (N = 49; one patient dropped out at experimental baseline). Subjects from the low-risk disease population exhibited <3mm of attachment loss, no periodontal probing depths of >4mm, and no radiographic alveolar bone loss. Disease susceptible subjects, exhibited at least 4 sites with evidence of radiographic bone loss, at least 4 sites with attachment loss of >3mm, and at least 4 sites with >4mm periodontal probing depth (Figure 8).

[0082] Subjects were excluded if they possessed a history of metabolic bone diseases such as rheumatoid arthritis or post-menopausal osteoporosis. Women who were pregnant were also excluded from the study.

[0083] All teeth except third molars were assessed for periodontal clinical measures by two calibrated examiners. These parameters included probing pocket depth (PD), clinical attachment level (CAL), plaque index (PI, dichotomously), gingival redness index (GRI, dichotomously), and bleeding on probing (BOP, dichotomously).

[0084] Standardized periapical digital radiographs (Schick Technologies, Long Island City, NY, USA) were taken in the posterior dentition of all the subjects using a parallel technique for the determination of alveolar bone height. Using a computer software measurement tool (Emago® Advanced, Oral Diagnostic Systems, Amsterdam, The Netherlands), the interproximal alveolar bone levels of both premolars and first and second molars were measured on a digital computer screen by one calibrated examiner. The distance from the alveolar bone crest to the cemento-enamel junction (CEJ) or the restoration margin reference was recorded as the radiographic alveolar bone level (RBL).

[0085] Subgingival plaque biofilm was collected from the mesiobuccal surfaces of all teeth and immediately placed into labeled vials containing 500µl of stabilizing buffer to prevent mRNA degradation (RNA Protect™, Ambion, Austin, TX) as previously described (Shelburne *et al.*, 2008, PLoS ONE 3, e1984). After vortexing for 30 seconds, the samples were stored at 4°C until they were sent to the laboratory for analysis.

[0086] The detection of *Aggregatibacter actinomycetemcomitans*, *Campylobacter rectus*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola* in pooled plaque samples were evaluated by real-time quantitative PCR (qPCR) as described (Mullally *et al.*, 2000, J Periodontal Res 35: 232-241; Shelburne *et al.*, 2000, J Microbiol Methods 39: 97-107) using primers specific for the hypervariable segments of the 16S rRNA genes of each bacterium (Table 8). The percentage of the total flora for each species was calculated by dividing the number of target organisms by the total number of bacteria as determined by qPCR using 16S rRNA primers that reacted with all bacterial species. Data are represented on a patient-based assessment.

Table 8. Primers for qPCR analysis of plaque biofilm bacteria.

Bacterial Species	Forward primer (5'-3')	SEQ ID NO	Reverse Primer (5'-3')	SEQ ID NO
<i>A. actinomycetemcomitans</i>	GGCAGTAGGCGGACCTT	1	ACCAGGGCTAAAGCCCAATC	2
<i>C. rectus</i>	TTTCGGAGCGTAAACTCCTTTTC	3	TTTCTGCAAGCAGACACTCTT	4
<i>F. nucleatum</i>	ACCAGCGTTTGACATCTTAGGAATG	5	AGCCATGCACCTGTCTTTAG	6
<i>P. intermedia</i>	AGATTGACGGCCCTATGGGT	7	CCGGTCCTTATTCGAAGGGTA	8
<i>P. gingivalis</i>	CATAGATATCACGAGGAACCTCCGATT	9	AAACTGTTAGCAACTACCGATGTGG	10
<i>T. forsythia</i>	GGGTGAGTAACGCGTATGTAACCT	11	ACCCATCCGCAACCAATAAA	12
<i>T. denticola</i>	CGTTCCTGGGCCTTGTACA	13	TAGCGACTTCAGGTACCCTCG	14
Universal	CCATGAAGTCGGAATCGCTAG	15	GCTTGACGGGCGGTGT	16

[0087] Unstimulated whole saliva was collected with passive drooling into sterile plastic tubes from all the subjects at the beginning of the screening appointment (Mandel *et al.*, 1976, Oral Sci Rev: 25-47). The collection was completed as soon as 2 mL of whole saliva was collected or a maximum of 15 minutes of sampling time had been reached. Subsequently, the samples were placed on ice, aliquoted and supplemented with a proteinase inhibitor combination of 1% aprotinin and 0.5% phenylmethanesulfonyl fluoride (PMSF) prior to storage at -80°C.

[0088] Protein biomarker levels were determined using colorimetric-based enzyme-linked immunosorbent assays (ELISAs), fluorescence-based protein microarrays, and radioimmunoassay (RIA), run according to manufacturer protocols. ELISAs (R&D Systems

Inc., Minneapolis, MN, USA) were used for measurement of MMP-8, MMP-9, calprotectin, and osteoprotegerin (OPG). Detection of the cytokines IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, tumor necrosis factor- α (TNF), and interferon (IFN)- γ was accomplished using a protein microarray (Whatman Inc., Florham Park, NJ, USA). Concentration of pyridinoline cross-links of type I collagen (ICTP) was determined using an RIA (Immunodiagnostic Systems Inc., Fountain Hills, AZ, USA).

[0089] Prior to each assay, whole saliva samples were thawed at room temperature (RT) and microcentrifuged for 5 min to obtain cell-free supernatant for analysis. In the case of the ELISAs, absorbance measurements (Molecular Devices Corporation, Sunnyvale, CA, USA) were collected using a primary signal at 450 nm with background subtraction of the 540 nm signal. A fluorescence scanner (Molecular Devices Corporation, Sunnyvale, CA, USA) was operated to collect Cy5 fluorescence signal from the cytokine protein microarrays. Data collection of the protein microarray signals was performed using Genepix Pro (Molecular Devices Corporation, Sunnyvale, CA, USA) software.

[0090] Basic demographics were summarized with means and proportions for each subject group; between-group comparisons were made with a one-way analysis of variance (ANOVA). Biomarker levels were summarized with medians for each group; between-group comparisons were made with a Kruskal-Wallis test. Areas Under the Curve (AUCs) for Receiver Operating Characteristic (ROC) curves were estimated non-parametrically (Bamber, 1975, Br J Math Stat Psychol 12: 387–415). Thresholds for biomarkers were pre-selected as those values for which sensitivity and specificity were as equal as possible. ROC curves and corresponding AUCs for multiple biomarker combinations were based upon predicted probabilities of diseased subjects from a logistic regression model in which a subject's biomarker levels were dichotomized as being either above or below their corresponding thresholds. Furthermore, the biomarkers and microbial gene biofilm levels were ranked in importance via Random Forest methods (Breiman, 2001, Machine Learning 45: 5-32). A statistical significance was defined as a $p < 0.05$.

[0091] Fifty-seven female (74% Caucasian) and 42 male (81% Caucasian) subjects were enrolled in the study ranging in age from 20 to 77 years. Following the recording of both periodontal clinical and radiographic parameters, the 99 subjects were stratified into four groups (Figure 8) (Borrell *et al.*, 2005, J Clin Periodontol 32 Suppl 6: 132-158; Tonetti *et al.*, 2005, Group C consensus report of the 5th European Workshop in Periodontology. J Clin Periodontol 32 Suppl 6: 210-213).

[0092] From the low-risk disease population, 18 subjects were stratified as healthy (Group 1) with no signs of periodontal breakdown and with BOP $\leq 20\%$. Thirty-two subjects were categorized as possessing gingivitis (BOP $>20\%$) and no alveolar bone loss (Group 2). From the disease susceptible population, 28 subjects exhibiting $< 30\%$ of sites with CAL of $> 2\text{mm}$ were classified as mild chronic periodontitis (Group 3), and 21 subjects were labeled as moderate-severe chronic periodontitis with $>30\%$ of sites with CAL of $>2\text{mm}$ (Group 4).

[0093] Dental and periodontal data (Table 9) were significantly different among the four groups for the mean number of teeth (25 - 28, $p<0.001$), BOP (12% - 64%, $p<0.001$), GRI (13% - 56%, $p<0.001$), presence of plaque biofilm (13% - 56%, $p<0.001$), mean probing depths (1.49mm - 3.03mm, $p<0.001$), sites with PD greater than 4mm (0% - 20%, $p<0.001$), mean AL (0.59mm - 2.93mm, $p<0.001$), and mean RBL (1.89mm - 4.33mm, $p<0.001$). Additionally, the prevalence of smoking was significantly higher in groups 3 and 4 (36% and 81% respectively, $p<0.001$). The demographics for age, gender, and ethnicity, however, were not statistically different and were balanced among the four groups.

Table 9. Patient demographics and clinical parameters stratified by level of disease.

	A	B	C	D	P-values comparing A, B, C & D		P-value comparing A&B vs C&D
	Healthy	Gingivitis	Mild Chronic Periodontitis	Moderate to Severe Chronic Periodontitis	Overall	Trend	
Number of Subjects	18	32	28	21	n/a	n/a	n/a
% Male	56	41	39	38	0.67	0.32	0.47
% White	78	78	68	86	0.54	0.80	0.78
% Smoker	0	19	36	81	< 0.001	< 0.001	< 0.001
Mean Number of Teeth	28	27	26	25	< 0.001	< 0.001	< 0.001
Mean Age	45	42	53	50	0.02	0.03	0.002
% BOP ^a	12	31	52	64	< 0.001	< 0.001	< 0.001
% GI ^b	13	22	49	56	< 0.001	< 0.001	< 0.001
% PI ^c	24	26	57	61	< 0.001	< 0.001	< 0.001
Mean PD ^d	1.49	1.65	2.29	3.03	< 0.001	< 0.001	< 0.001
% Sites PD $\geq 5\text{mm}$	0	0	7	20	< 0.001	< 0.001	< 0.001
Mean CAL ^e	0.59	0.72	1.69	2.93	< 0.001	< 0.001	< 0.001
Mean BL ^f	1.89	2.00	3.13	4.33	< 0.001	< 0.001	< 0.001

^a Bleeding on probing (%)

^b Gingival index (%)

^c Plaque index (%)

^d Periodontal probing depth

^e Clinical attachment loss

^f Radiographic alveolar bone level

Example 3

[0094] Data from the analysis of putative biomarkers of periodontal disease are shown in Table 10. Given that the majority (>70%) of the subjects failed to reveal protein levels of IL-5 and IFN- γ in their whole saliva, these proteins were not included.

[0095] Median levels of protein concentrations were increased in subjects with advancing stages of periodontal disease as compared to the healthier individuals for MMP-8 ($p<0.001$), MMP-9 ($p=0.001$), calprotectin ($p=0.023$). Increased levels of osteoprotegerin (OPG) demonstrated a significant ability to predict health ($p=0.007$; Table 10). Various trends were noted for other biomarkers including ICTP, IL-1, and IL6, but these were not significant. Random Forest methods were ranking the importance of MMP-8 with a score of 7.1 and OPG with a score of 6.3 reflecting the highest importance level amongst the biomarkers in this dataset.

Table 10. Median levels (ranges) and diagnostic ability of salivary biomarkers and plaque biofilm pathogens.

		A	B	C	D	P-values comparing A, B, C & D	P-values comparing A & B vs. C & D	AUC	Importance Score via Random Forest
Biomarker	Conc.	Healthy Median (range)	Gingivitis Median (range)	Mild Chronic Periodontitis Median (range)	Moderate & Severe Chronic Periodontitis Median (range)				
MMP8	ng/mL	23.6 (2.5, 322.5)	54.1 (1, 473.9)	129.9 (8.5, 978.9)	203.8 (10.1, 2681.1)	<0.001	<0.001	0.75	7.1
OPG	pg/mL	2.3 (1.4, 6.6)	2.7 (1.2, 6.2)	1.9 (0.2, 10.1)	1.6 (0.5, 11.8)	0.056	0.007	0.62	6.3
MMP9	ng/mL	106.4 (10, 1185.7)	225.8 (4.9, 1732.2)	301.6 (4.6, 3348.1)	780.8 (10.4, 9778.2)	0.002	0.001	0.72	5.1
Calprotectin	ng/mL	3.0 (1.3, 10)	3.5 (0, 24.6)	4.3 (0, 17.8)	5.4 (1.7, 97.6)	0.082	0.023	0.68	4.7
IL1 β	pg/mL	158.6 (0, 6000)	206.7 (0, 3856.8)	247.5 (24.1, 3120)	462.2 (15.7, 6000)	0.157	0.059	0.72	3.7
ICTP	ng/mL	0.9 (0, 4)	0.8 (0, 4)	0.6 (0, 5.4)	0.9 (0, 13.9)	0.195	0.185	0.58	3.2
IL6	pg/mL	0.0 (0, 1915)	22.1 (0, 8784.9)	14.6 (0, 5259.7)	88.7 (0, 10816.9)	0.127	0.092	0.71	2.2
IL10	pg/mL	881.4 (0, 11088.8)	120.6 (0, 45488.9)	1153.1 (0, 24581.4)	1445.1 (0, 30633.1)	0.618	0.329	0.68	1.9
TNF α	pg/mL	9.8 (0, 1788.3)	0.0 (0, 3720.5)	8.1 (0, 4370.2)	0.0 (0, 8212.7)	0.483	0.954	0.64	1.8
IL13	pg/mL	14.3 (0, 83151.1)	0.0 (0, 92423.8)	0.0 (0, 76046)	169.9 (0, 75445.2)	0.780	0.783	0.64	1.5
IL4	pg/mL	0.0 (0, 5315.1)	0.0 (0, 6579.3)	54.4 (0, 14588)	69.5 (0, 11714.3)	0.377	0.086	0.71	1.3
IL2	pg/mL	0.0 (0, 3718.1)	0.0 (0, 6000)	8.0 (0, 6205.5)	0.0 (0, 14400.1)	0.421	0.178	0.69	1.2
Pathogen									
<i>T. denticola</i>	%	0.11 (0, 0.54)	0.10 (0, 2.95)	1.53 (0, 5.25)	2.34 (0.79, 6.63)	< 0.001	< 0.001	0.86	13.7
<i>P. gingivalis</i>	%	0.05 (0, 0.9)	0.04 (0, 0.66)	0.53 (0, 2.36)	1.00 (0.43, 3.24)	< 0.001	< 0.001	0.84	9.6
<i>T. forsythia</i>	%	0.09 (0, 0.88)	0.07 (0, 0.8)	0.71 (0, 3.16)	1.26 (0.11, 3.55)	< 0.001	< 0.001	0.85	8.4
<i>P. intermedia</i>	%	0.11 (0, 1.17)	0.20 (0, 1.99)	0.82 (0, 3.77)	1.85 (0, 3.5)	< 0.001	< 0.001	0.79	6.7
<i>C. rectus</i>	%	0.00 (0, 1.22)	0.00 (0, 1.18)	0.66 (0, 2.82)	1.32 (0, 3.34)	0.001	< 0.001	0.74	4.7
<i>F. nucleatum</i>	%	2.96 (0, 8.27)	2.33 (0, 7.32)	3.29 (0, 10.74)	3.30 (0, 9.56)	0.251	0.196	0.59	3.9
<i>E. corrodens</i>	%	0.00 (0, 0.96)	0.00 (0, 1.04)	0.00 (0, 1.32)	0.00 (0, 0.1)	0.697	0.259	0.56	0.3

AUC - Area Under the Curve

[0096] Further analysis was computed with a subset of biomarkers demonstrating 1) high Random Forest importance scores; 2) relative low p values; and 3) high AUCs. The diagnostic properties of specific thresholds that gave nearly equal levels of sensitivity and specificity for the selection of biomarkers. MMP-8, MMP-9 and calprotectin demonstrated significant abilities to predict disease category (ORs ranged from 5.3 - 2.7) for these markers as shown in Table 11.

Table 11. Diagnostic properties of specific thresholds of selected salivary biomarkers and plaque biofilm pathogens.

Biomarker		Threshold	Above Threshold	Periodontitis		Sens	Spec	Odds Ratio	95% CI
				No (n)	Yes (n)				
MMP8	ng/mL	87.0	-	28	12	0.69	0.70	5.3	(2.0, 13.7)
			+	12	27				
MMP9	ng/mL	240.0	-	28	12	0.69	0.70	5.3	(2.0, 13.7)
			+	12	27				
Calprotectin	ng/mL	3.6	-	25	15	0.62	0.63	2.7	(1.1, 6.6)
			+	15	24				
IL6	pg/mL	22.4	-	24	16	0.59	0.60	2.2	(0.9, 5.3)
			+	16	23				
IL1 β	pg/mL	235.8	-	22	18	0.54	0.55	1.4	(0.6, 3.5)
			+	18	21				
IL10	pg/mL	520.9	-	22	18	0.54	0.55	1.4	(0.6, 3.5)
			+	18	21				
OPG	pg/mL	2.0	-	17	22	0.44	0.43	0.6	(0.2, 1.4)
			+	23	17				
ICTP	ng/mL	0.7	-	16	23	0.41	0.40	0.5	(0.2, 1.1)
			+	24	16				
Pathogen									
<i>T. denticola</i>	%	0.2	-	33	7	0.82	0.83	21.6	(6.8, 68.4)
			+	7	32				
<i>T. forsythia</i>	%	0.1	-	32	8	0.80	0.80	15.5	(5.2, 46.4)
			+	8	31				
<i>P. gingivalis</i>	%	0.1	-	31	8	0.80	0.78	13.3	(4.6, 39.1)
			+	9	31				
<i>P. intermedia</i>	%	0.4	-	29	11	0.72	0.73	6.7	(2.5, 18)
			+	11	28				
<i>C. rectus</i>	%	0.1	-	25	15	0.62	0.63	2.7	(1.1, 6.6)
			+	15	24				
<i>F. nucleatum</i>	%	2.8	-	24	16	0.59	0.60	2.2	(0.9, 5.3)
			+	16	23				
<i>E. corrodens</i>	%	0.0	-	35	31	0.21	0.88	1.8	(0.5, 6.1)
			+	5	8				

Sens Sensitivity

Spec Specificity

CI Confidence Interval

[0097] Table 11 demonstrates the median levels as a percentage of the flora of selected red and orange complex organisms for their ability to identify periodontal disease category. An even greater diagnostic ability of these organisms was demonstrated as compared to those revealed by the salivary biomarkers. When comparing low risk and high risk groups, *T.*

denticola, *P. gingivalis*, *T. forsythus*, *P. intermedia*, and *C. rectus* all demonstrated significant differences between groups ($p < 0.001$). *F. nucleatum* and *E. corrodens* did not demonstrate a significant relationship. When the diagnostic properties were evaluated for the pathogens demonstrating significant differences between groups, good sensitivity and specificity for disease category were shown as well as ORs (21.6 - 2.7) for *T. denticola*, *P. gingivalis*, *T. forsythus*, *P. intermedia*, and *C. rectus* (Table 11).

Example 4

[0098] Multi-analyte assessments were performed using various combinations of salivary biomarkers and plaque biofilm levels (Figure 9). For example, when MMP-8 and calprotectin were combined to predict "high-risk" periodontal status, an AUC of 0.74 was found with a corresponding OR = 3.9 (95% CI 1.3, 11.6) (Figure 9A). When multiple biomarkers were combined such as MMP-8, OPG and ICTP, the AUC was increased to 0.75 with OR = 10.1 (95% CI = 1.2, 84.8) (Figure 9C). When the microbial biofilm was combined with the biomarkers, the predictive values increased markedly. Figure 9D demonstrates the combination of MMP-8 and *T. denticola* with a resultant AUC = 0.88 (OR = 24.6, 95% = CI 5.2, 116.6). Further improvements in the OR were noted when several pathogens were combined. Given the relatively small sample of 99 subjects, OR could not be determined for many combinations given that all cases of periodontal disease category were correctly identified when comprehensive combinations were chosen and were considered infinite for these permutations (Table 12, below). These results suggest that although the study of 99 subjects was able to determine differences in biomarker/biofilm levels to identify disease category, a much larger sample is needed to generate ORs that can be usable given the high level of accuracy demonstrated in this patient cohort.

Table 12. Positive and Negative Predictive Values of specific thresholds of selected salivary biomarkers and plaque biofilm pathogens.

Biomarker		Threshold	Above Threshold	Periodontitis		PPV	NPV
				No (n)	Yes (n)		
MMP-8	ng/mL	87.0	-	28	12	0.69	0.70
			+	12	27		
MMP-9	ng/mL	240.0	-	28	12	0.69	0.70
			+	12	27		
Calprotectin	ng/mL	3.6	-	25	15	0.62	0.63
			+	15	24		
IL-6	pg/mL	22.4	-	24	16	0.59	0.60
			+	16	23		
IL-1 β	pg/mL	235.8	-	22	18	0.54	0.55
			+	18	21		
IL-10	pg/mL	520.9	-	22	18	0.54	0.55
			+	18	21		
OPG	pg/mL	2.0	-	17	22	0.43	0.44
			+	23	17		
ICTP	ng/mL	0.7	-	16	23	0.40	0.41
			+	24	16		
Pathogen							
<i>T. denticola</i>	%	0.2	-	33	7	0.82	0.83
			+	7	32		
<i>T. forsythia</i>	%	0.1	-	32	8	0.80	0.80
			+	8	31		
<i>P. gingivalis</i>	%	0.1	-	31	8	0.78	0.80
			+	9	31		
<i>P. intermedia</i>	%	0.4	-	29	11	0.72	0.73
			+	11	28		
<i>C. rectus</i>	%	0.1	-	25	15	0.62	0.63
			+	15	24		
<i>F. nucleatum</i>	%	2.8	-	24	16	0.59	0.60
			+	16	23		
<i>E. corrodens</i>	%	0.0	-	35	31	0.62	0.53
			+	5	8		

PPV - Positive Predictive Value

NPV - Negative Predictive Value

WHAT IS CLAIMED:

1. A method to determine probability of an oral disease state comprising the step of determining the levels of two or more biomarkers in a sample from a first individual, said levels of said two or more biomarkers indicating the probability of said oral disease state.
2. The method of claim 1 which is diagnostic and said levels of said two or more biomarkers are indicative of oral disease if said levels of said two or more biomarkers from said first individual are elevated compared to levels of identical biomarkers from a second individual.
3. The method of claim 1 which determines susceptibility to oral disease and said levels of said two or more biomarkers are indicative of susceptibility to oral disease if said levels of said two or more biomarkers from said first individual are elevated compared to levels of identical biomarkers from a second individual.
4. The method of claim 1 wherein said levels of said two or more biomarkers are indicative of susceptibility to oral disease if said levels of said two or more biomarkers from said first individual are elevated compared to biomarker levels of the first individual measured at an earlier time point.
5. The method of claim 1 wherein said levels of said two or more biomarkers are indicative of progression of oral disease if said levels of said two or more biomarkers from said first individual are elevated compared to biomarker levels of the first individual measured at an earlier time point.
6. The method of claim 1 which determines effectiveness of oral disease treatment wherein said levels of said two or more biomarkers are indicative of effective oral disease treatment if said levels of said two or more biomarkers from said first individual are decreased compared to levels of identical biomarkers from the same individual measured at an earlier time point.
7. The method of claim 1 wherein the probability of diagnosing said disease is equal to or greater than 70%.

8. The method of claim 1 wherein the probability of diagnosing said disease is equal to or greater than 80%.
9. The method of claim 1 wherein the probability of diagnosing said disease is equal to or greater than 90%.
10. The method of claim 1 wherein the levels of two biomarkers are determined.
11. The method of claim 1 wherein the levels of three, four, or five biomarkers are determined.
12. The method of claim 1 wherein the two or more biomarkers are selected from the group consisting of *Aggregatibacter actinomycetemcomitans*, *Campylobacter rectus*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, matrix metalloproteinase-8 (MMP-8), matrix metalloproteinase-9 (MMP-9), osteoprotegerin (OPG), type I collagen pyridinoline cross-linked telopeptide (ICTP), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), interleukin-4 (IL-4), interleukin-10 (IL-10), interleukin-2 (IL-2), interleukin-13 (IL-13), calprotectin, tumor necrosis factor α (TNF α) and combinations thereof.
13. The method of claim 7 wherein the two or more biomarkers include the combinations of biomarkers as set out in Table 1.
14. The method of claim 8 wherein the two or more biomarkers include the combinations of biomarkers as set out in Table 2.
15. The method of claim 9 wherein the two or more biomarkers include the combinations of biomarkers as set out in Table 3.
16. The method of claim 1 wherein the probability is calculated in a method comprising the steps of:
 - determining the levels of two or more biomarkers in said first individual and a second individual,
 - generating a receiver operating characteristic (ROC) curve, and

calculating area under said ROC curve (AUC), said area providing the probability of said oral disease.

17. The method of claim 1 wherein the sample is selected from the group consisting of a bodily fluid, tissue and organ.

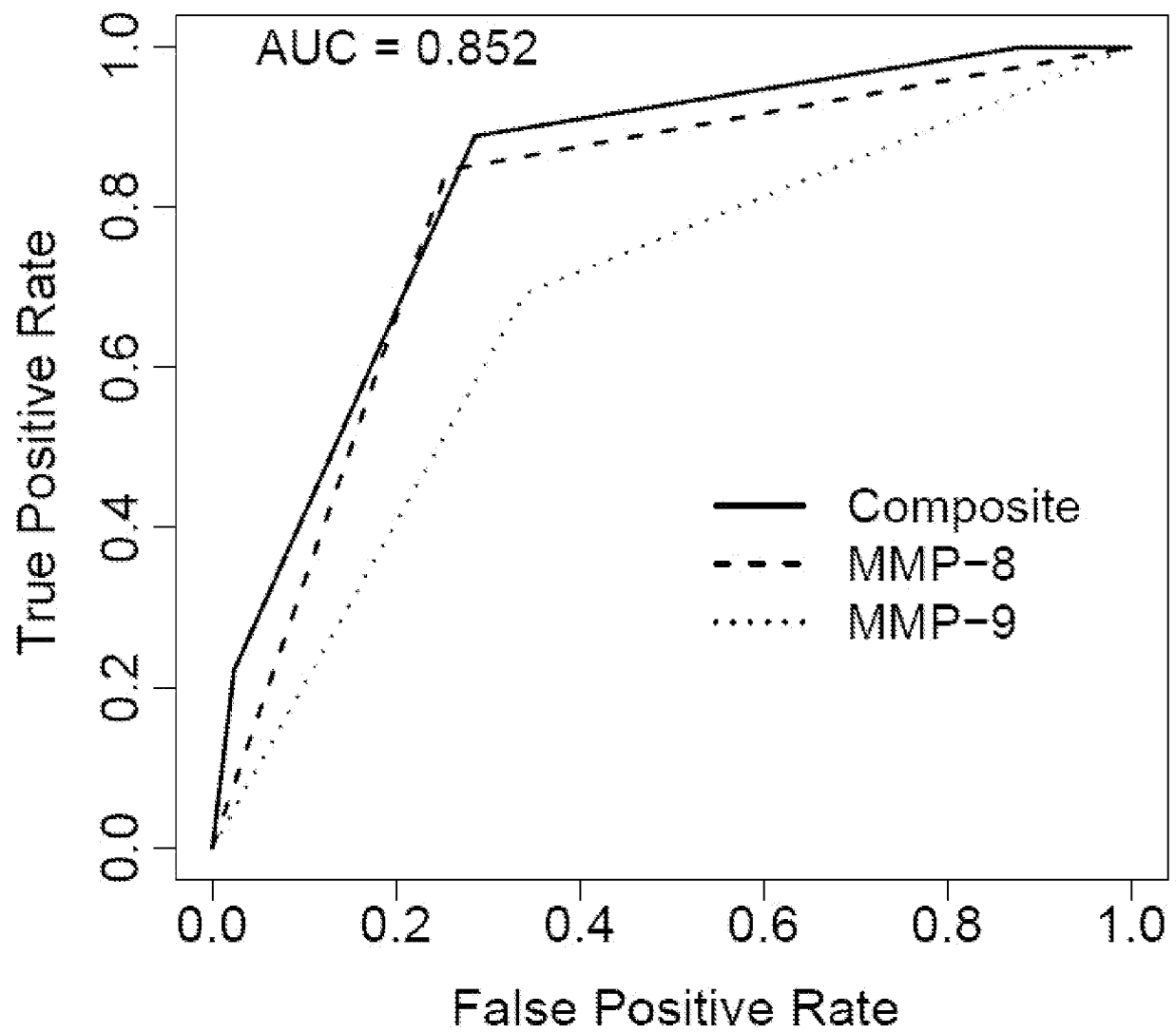
18. The method of claim 17 wherein the fluid is saliva.

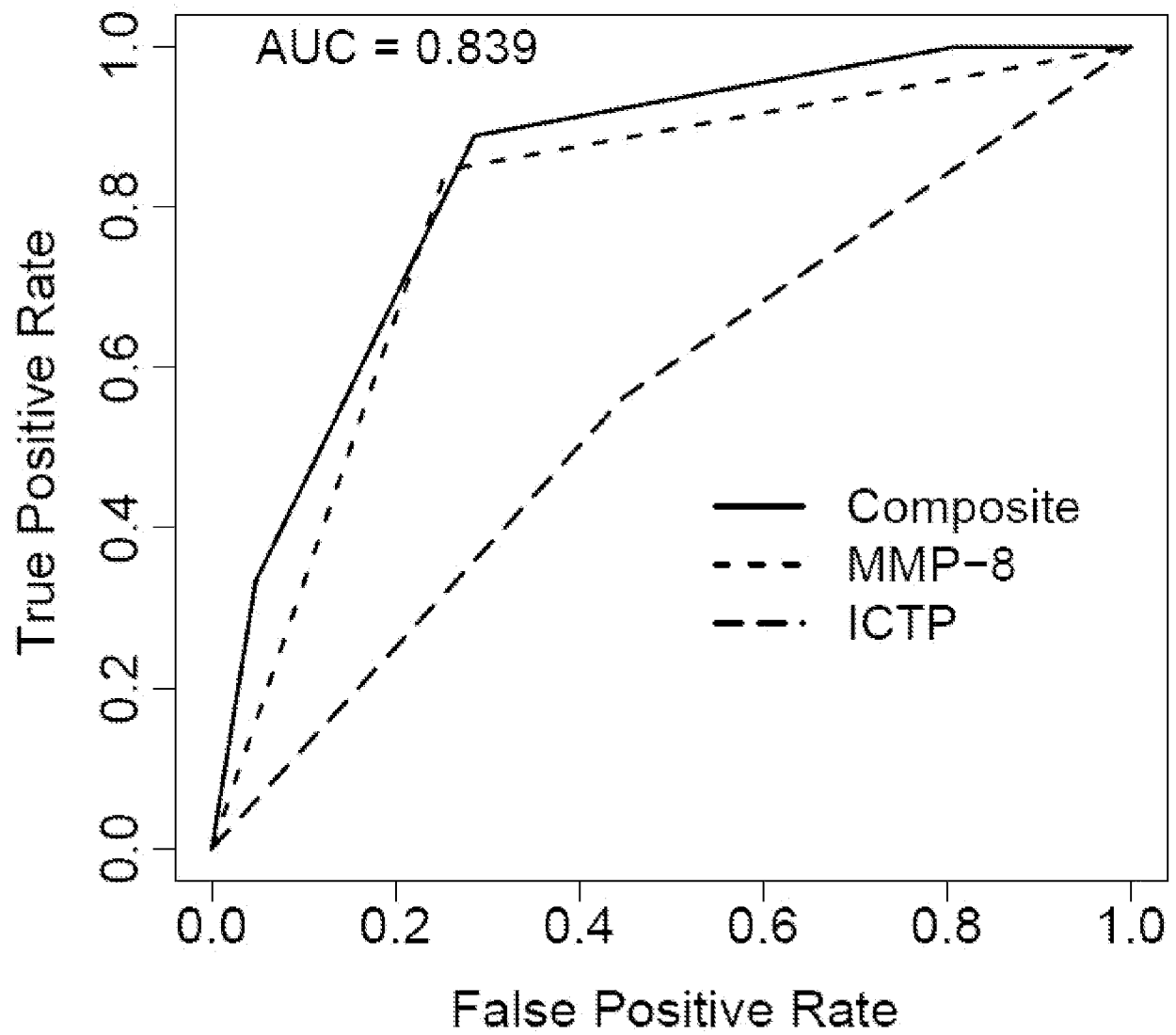
19. The method of claim 1 wherein the biomarker levels are biomarker protein levels in the sample.

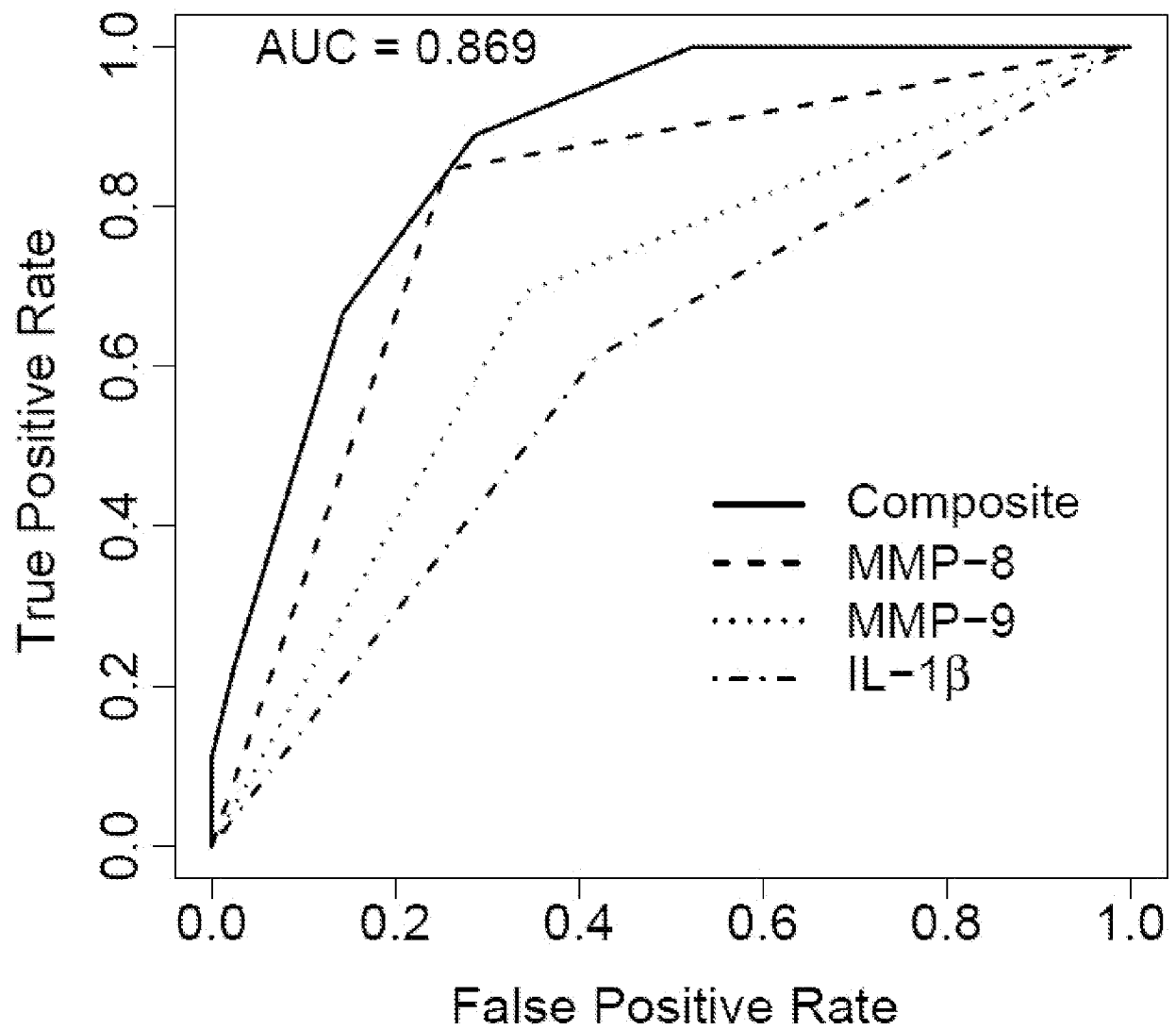
20. The method of claim 1 wherein said oral disease is periodontal disease.

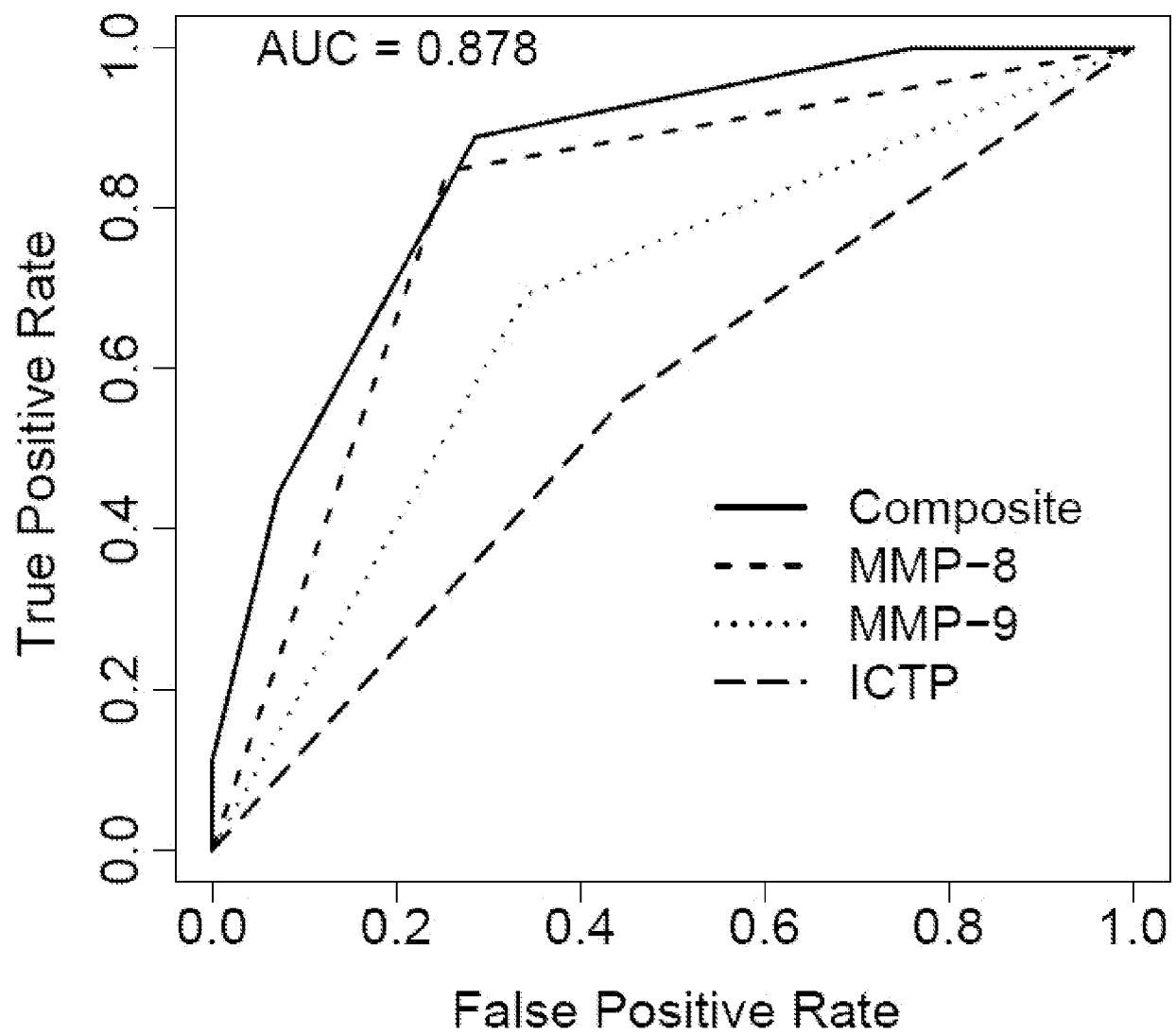
21. The method of claim 1 wherein said oral disease is peri-implant disease.

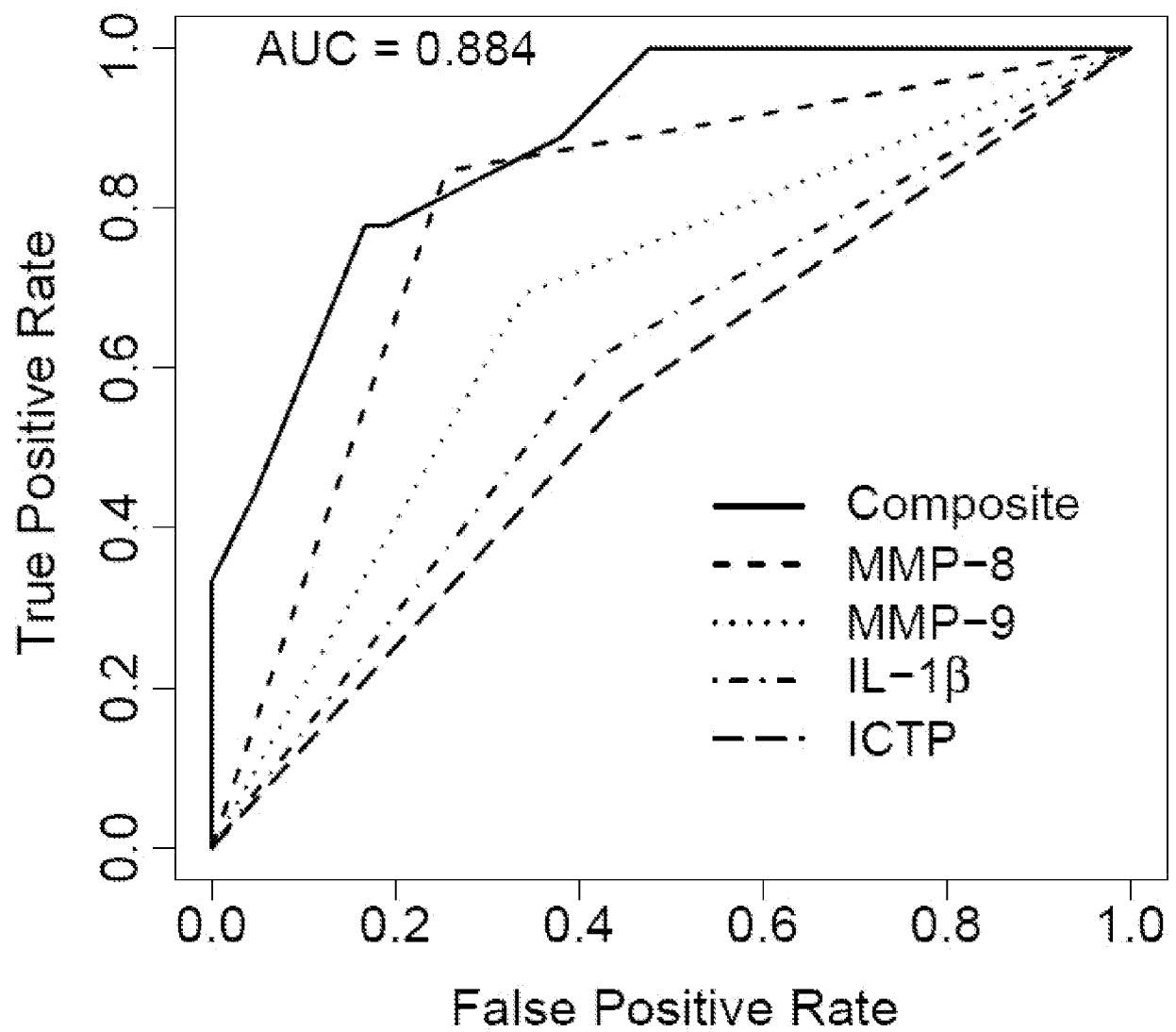
22. A kit for carrying out the method of claim 1, the kit comprising: a) a sterile plastic tube for sample collection, and b) one or more components selected from the group consisting of one or more reagents for performing the assay, a calibration standard and a quality control sample.

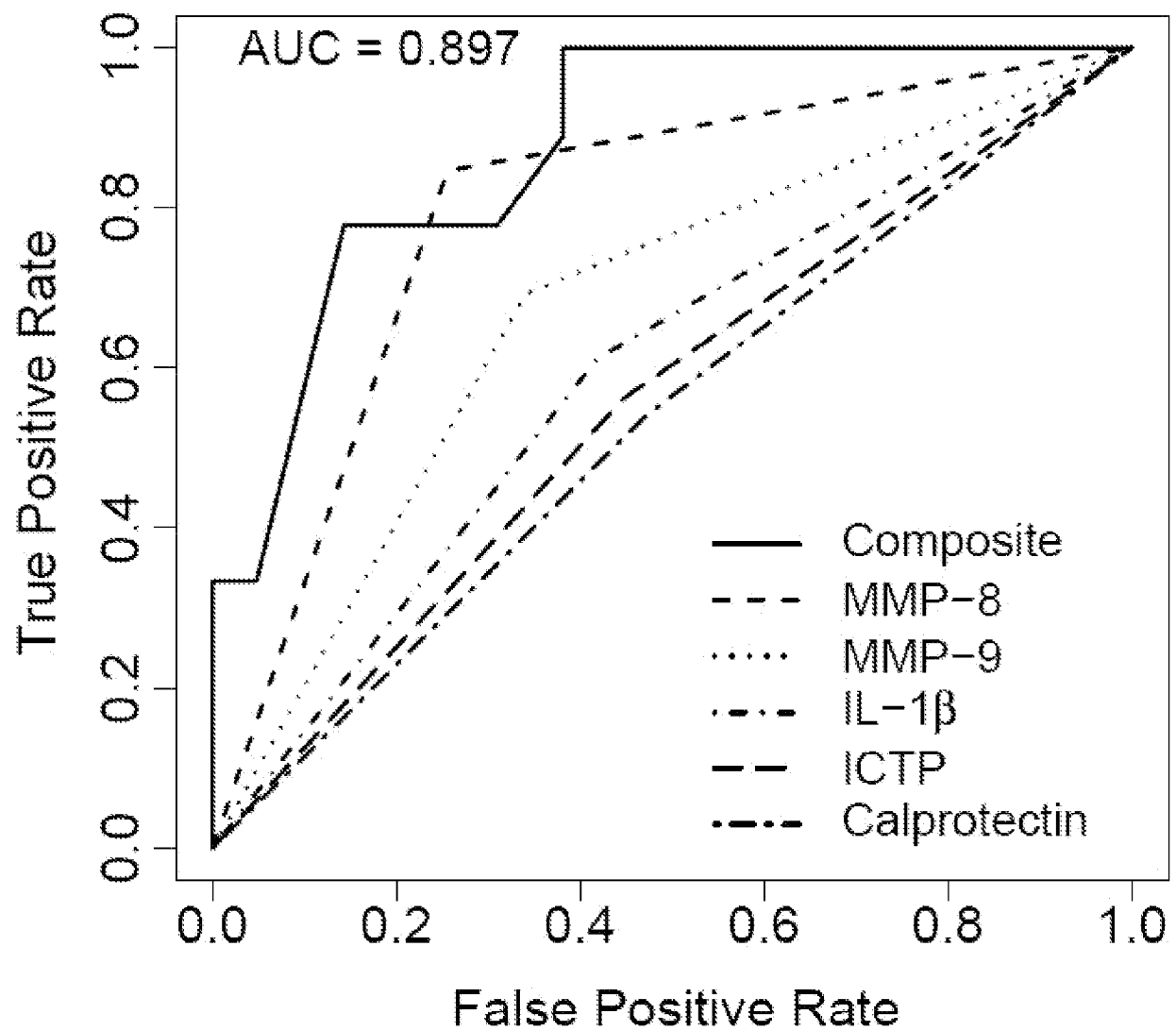
**Figure 1**

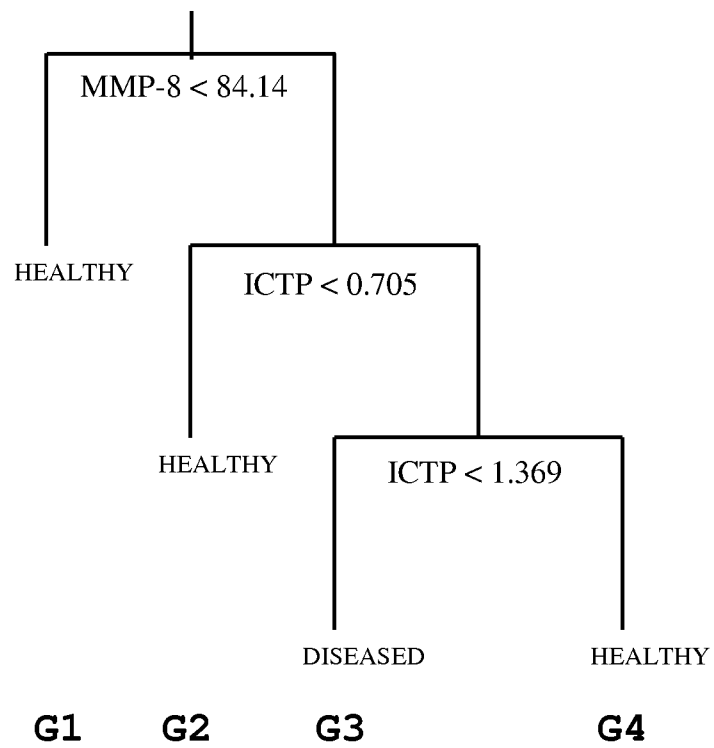
**Figure 2**

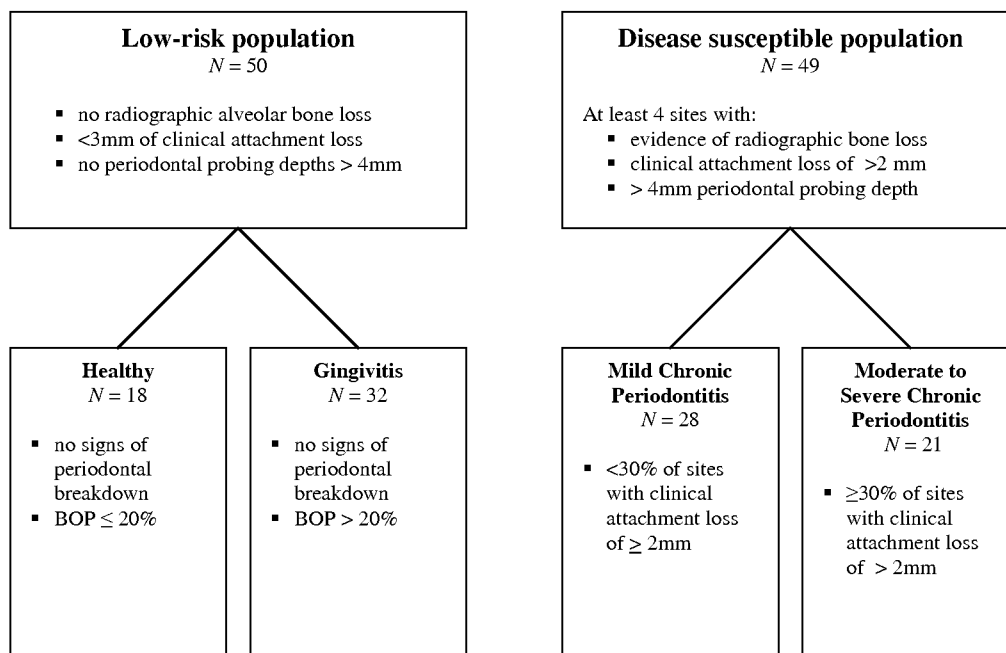
**Figure 3**

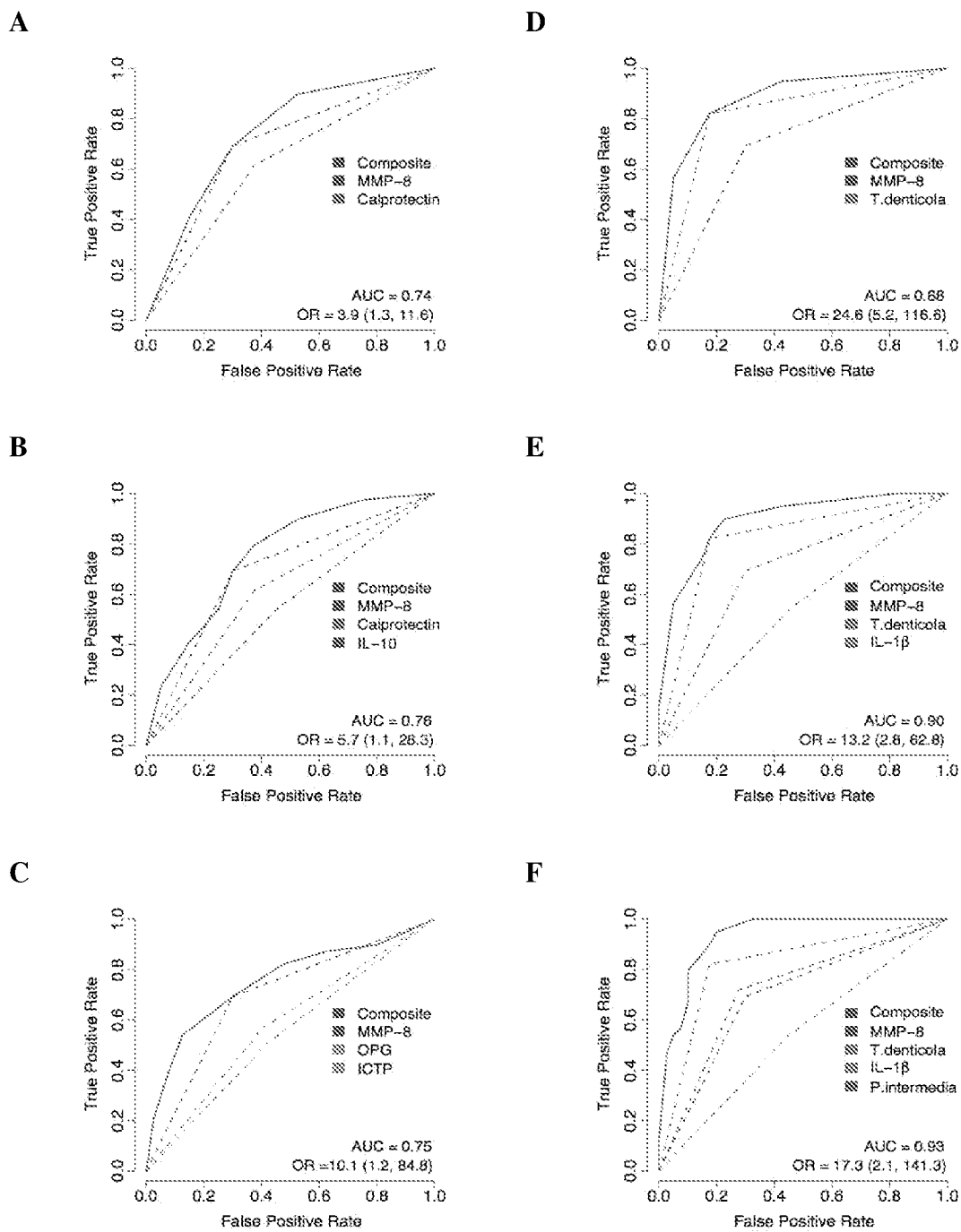
**Figure 4**

**Figure 5**

**Figure 6**

**Figure 7**

**Figure 8**

**Figure 9**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/71596

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12Q 1/68; C12Q 1/00 (2008.04)

USPC - 435/6; 435/4

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
435/6; 435/4Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
435/6 436/86 435/4; 435/188 435/7.1 435/7.9 435/7.93 435/7.94Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Dialog Classic Web (344,347-349,371,652,654,345,351), Google: oral, disease, saliva, biomarker(s), periodontal, peri-implant, curve, area, Aggregatibacter, Campylobacter

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2004/0181344 A1 (Stephanopoulos, et al.) 16 Sep 2004 (16.09.2004); abstract; claims 11 and 21; para [0010], [0021], [0022], [0063], [0281], [0252], [0257], [0271], [0276], [0024], [0126], [0023], [0055], [0045], [0268], [0014], [0084]	1-10, 17-22 ----- 12, 16
Y	US 6,143,506 A (Golub, et al.) 07 Nov 2000 (07.11.2000); col 3, ln 50-60	12
Y	US 2001/0023324 A1 (Pronovost, et al.) 20 Sep 2001 (20.09.2001); para [0167], [0171]	16

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 December 2008 (12.12.2008)

Date of mailing of the international search report

23 DEC 2008

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/71596

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I, claims 1-10, 12, 16-22, drawn to a method to determine probability of an oral disease state comprising the step of determining the levels of two biomarkers in a sample from an individual, wherein claim 12 is limited to *Aggregatibacter actinomycetemcomitans* and *Campylobacter rectus*.

Group II+ claims 1-22. Should additional fees be paid, Applicant is invited to elect a combination of biomarkers to be searched.

The inventions listed as Groups I and II+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

--continued on next supplemental sheet----

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Group I, claims 1-10, 12, 16-22, wherein claim 12 is limited to *Aggregatibacter actinomycetemcomitans* and *Campylobacter rectus*.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/US 08/71596

***** SUPPLEMENTAL PAGE *****

Continuation of Box No. III

Although Groups I and II+ do share the technical feature of determining the levels of at least two biomarkers of an oral disease in a sample from an individual, this shared technical feature does not represent a contribution over the prior art. Specifically, the article entitled "Treponema socranskii, Treponema denticola, and Porphyromonas gingivalis are associated with severity of periodontal tissue destruction" by Takeuchi et al. (J Periodontol. 2001, 72(10):1354-63) teaches that "T. socranskii, T. denticola, and P. gingivalis were frequently detected in periodontitis patients by PCR. The prevalence of these 3 microorganisms was correlated with various clinical parameters. Taken together, our findings suggest that T. socranskii, T. denticola, and P. gingivalis are associated with the severity of periodontal tissue destruction" (abstract), thereby anticipating claims 1-10 and 12 of Group II+, drawn to determination of at least two biomarkers T. denticola, and P. gingivalis. As the above method was known at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I and II+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.