ARIC Manuscript Proposal # 3194

PC Reviewed: 7/10/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Establishing Clinical Metrics for Precision Oral Health.

b. Abbreviated Title (Length 26 characters):
Precision Oral Health

2. Writing Group:
Writing group members:
Steven Offenbacher, Kevin Moss, Thiago Morelli, Di Wu, James Beck.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __SO___ **[please confirm with your initials electronically or in writing]**

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We invite ARIC investigator(s) to participate in this manuscript

3. Timeline: Very quickly (about two weeks). The results in this manuscript essentially have been published in previous ARIC papers. The only part that will change in this manuscript is the periodontal phenotype. Please see rationale section below.

4. Rationale: The World Workshop on Periodontal Disease Classification (WW-2017) was held at the American Dental Association Headquarters in November, 2017. These workshops occur approximately every ten years and the changes in disease classification are disseminated to dental schools and dental practitioners world-wide and training about periodontal disease is based on the new classification system. As part of the World Workshop on Periodontal Disease Classification (WW-2017), a seminal paper by Tonetti, Greenwell, and Kornman[1] introduced a multidimensional staging and grading system as a framework for reclassifying chronic periodontitis. This schema is similar to the method used in oncology or rheumatology, in which "staging" is based upon the severity of disease and complexity of case management while "grading" speaks to biological features, such as the predicted rate of disease progression that, as corollary, relates to the risk for tooth loss and for becoming edentulous. Furthermore, grading should reflect the impact of person-level risk factors and potential threats to general health. Specifically, the authors proposed a new nosological structure that included distinct classes of disease that reflect a diagnosis that are referred to as Stages, but also a designation of Grade of disease for each diagnostic stage that reflect risk for tooth loss and other risk factors, such as smoking and diabetes. Furthermore, the proposed staging and grading was tasked with the requirement that it should reflect prognosis, as well as the complexity of treatment needs, including recommendation for referral to assist the clinician in case management. While this novel system has great potential for disease classification that could support the concept of precision dentistry, it currently has not been validated using patient data, nor does it accommodate mutually exclusive definitions of health or gingivitis.

Independently, we have been developing an agnostic, databased approach to define classes of periodontal conditions that include the spectrum of clinical presentations of health and disease that also incorporates missing teeth. This relatively new concept for disease classification successfully identified seven independent bins or classes of individuals with similar clinical traits. These classes of disease incorporated levels of tooth-loss, as well as tooth-specific recession, biotype and reduced periodontium assessments; in addition to the traditional clinical measures. Using Latent Class Analyses (LCA) we created seven latent (Hidden) classes, which included three new classes that were associated with mild tooth loss and very high GI scores, moderate tooth loss with reduced periodontium, and severe tooth loss. We called this group of seven disease conditions Periodontal Profile Classes (PPC) and the individual diagnoses were named Health, Mild Disease, High Gingival Inflammation (High GI), Tooth Loss, Moderate (Posterior) Disease, Severe Tooth Loss, and Severe Disease. A tooth profile class (TPC), was also derived using LCA[2] and remains applicable in this World Workshop model. Fundamentally, the model builds upon seven types of periodontal status seen around individual teeth as determined agnostically, plus missing teeth. These seven TPCs include teeth that are: Healthy, have Recession, have Crowns, have a Hi Gingival Index, have Interproximal Attachment Loss, have a Reduced Periodontium, and Severe disease (probing and attachment loss)[2]. This body of work is detailed in five publications that describe (1) the methods used in deriving the PPCs as well as a similar process applied at the tooth level (TPC)[2] (2) risk for disease progression and tooth loss for each PPC and derivation of the person-level Index of Periodontal Risk (IPR)[3]; (3) the relationships between PPCs and prevalent systemic conditions (diabetes, CHD, stroke) as well as measures of systemic inflammation (CRP, IL-6)[4]; (4) relationships between PPCs and incident stroke[5]; and (5) an overview of the entire project including future work and the potential application of the PPC for clinical dentistry[6]. At this point, the new Stages and Grades schema, while logical, has not been tested using data

representing actual clinical disease patterns. The purpose of this paper is to assess the validity of the Stages and Grades system proposed by the World Workshop using clinical findings from our PPC studies harmonizing PPCs with Stages and IPR scores as Grades.

5. Main Hypothesis/Study Questions: Will the new World Workshop Model be supported by patterns of health and disease that occurred in the ARIC visit 4 examination?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

We will use the ARIC visit 4 dental examination excluding anyone without a periodontal examination (6,793 respondents). This is the same group we used to conduct previous analyses that derived the PPC phenotypes[2].

Nomenclature, Stages, and Grades:

We have already completed the process of adapting our PPC phenotypes to the WW-2017 Stages and Grades schema. Briefly, the previous seven PPC disease states become Stages 0-6 and the Grades of disease were defined using the following IPR cut-off-values. Grade 0 = IPR<10, Grade 1 = IPR 10 to <20, Grade 2 = IPR 20 to <30, Grade 3 = IPR 30 to <40 and Grade 4 is IPR 40 or greater. Stages were assigned first, and then using IPR as a risk indicator, the Grade was assigned for those within each Stage. Importantly, the agnostic LCA assignments had no *a priori* assumptions of health or gingivitis, but rather were applied to the entire ARIC test population to permit the algorithm to assign traits that best described Stage and Grade strata that we can now interpret as being most consistent with our traditional concepts of health, gingivitis and periodontitis. The following table is an example of how our conversion of PPC to Stage and Grade will look to determine the distribution of demographics and risk factors for periodontal disease by stage and grade:

Table 1: Demographics and Risk Factors by Stage and Grade

STAGES	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Stage 0: Health (n)						
% Male						
% African American						
% Diabetic						
% Smoker						
Mean Age						
Stage 1: Mild Perio (n)						
% Male						
% African American						
% Diabetic						
% Smoker						
Mean Age						
Stage 2 Mod Perio (n)						
% Male						
% African American						
% Diabetic						

% Smoker **Mean Age**						
Stage 3 Severe Perio (n) **% Male** **% African American** **% Diabetic** **% Smoker** **Mean Age**						
Stage 4 Mild TL/High GI(n) **% Male** **% African American** **% Diabetic** **% Smoker** **Mean Age**						
Stage 5 Mod TL/Reduced Perio (n) **% Male** **% African American** **% Diabetic** **% Smoker** **Mean Age**						
Stage 6 Severe TL (n) **% Male** **% African American** **% Diabetic** **% Smoker** **Mean Age**						
All Stages **% Male** **% African American** **% Diabetic** **% Smoker** **Mean Age**						

Statistical Analysis:

All statistical analyses will be performed with SAS 9.4 (SAS Institute, Cary, NC, USA). We plan to use PROC MEANS to calculate percents. PROC GENMOD will be used to calculate relative risk. The p-trend statistic will be calculated using Proc REG. P values <0.05 will be considered significant.

References

1. Tonetti MS, Greenwell H, Kornman KS. Periodontitis Case Definition: Framework for Staging and Grading the Individual Periodontitis Case. *J Periodontol* 2018; In Press.
2. Morelli T, Moss K, Beck J, Preisser JD, Wu D, Divaris K, Offenbacher S. . Derivation and validation of the Periodontal and Tooth Profile Classification System for patient stratification.". *J Periodontol* 2017;88:153-165.
3. Morelli T, Moss K, Preisser JS, Beck JD, Divaris K, Wu D, Offenbacher S. Periodontal profile classes predict periodontal disease progression and tooth loss. *J Periodontol* 2018;89(2):148-156.

4. Beck JD, Moss K, Morelli T, Offenbacher S. Periodontal Profile Class (PPC) is associated with prevalent diabetes, coronary heart disease, stroke, and systemic markers of C-Reactive Protein and Interleukin 6. *J Periodontol* 2018;89(2):157-165.
5. Sen S, Giamberadino L, Moss K, Morelli T, Rosamond WD, Gottesman RF, et, al. Perioodntal Disease, Regular Dental Care Use, and Incident Ischemic Stroke. *Stroke* 2018;49:355-362.
6. Beck JD, Moss K, Morelli T, Offenbacher S. In search of appropriate measures of periodontal status: The Periodontal Profile Phenotype (P^3) System. *J Periodontol* 2018;89(2):166-175.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? __X__ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes _X___ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__X____ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?
The ARIC manuscripts that contain similar results, but with a different characterization of the periodontal phenotype are:

Morelli T, Moss K, Beck J, Preisser JD, Wu D, Divaris K, Offenbacher S. . Derivation and validation of the Periodontal and Tooth Profile Classification System for patient stratification.". *J Periodontol* 2017;88:153-165.

Morelli T, Moss K, Preisser JS, Beck JD, Divaris K, Wu D, Offenbacher S. Periodontal profile classes predict periodontal disease progression and tooth loss. *J Periodontol* 2018;89(2):148-156.

Beck JD, Moss K, Morelli T, Offenbacher S. In search of appropriate measures of periodontal status: The Periodontal Profile Phenotype (P^3) System. *J Periodontol* 2018;89(2):166-175.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* __ 1996.01_)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __x__ No.