




# Interleukin 1 genetic tests provide no support for reduction of preventive dental care

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**A** study of dental benefits claims concluded that genetic polymorphisms in the interleukin 1 (IL-1) genes *IL1A* and *IL1B* (the “PST” genetic test) identified “high-risk” patients who benefitted significantly more than “low-risk” patients from receiving a second annual preventive visit by reducing tooth

extractions.<sup>1</sup> The authors of the study concluded

 Supplemental material is available online.

that the data justify providing 2 annual preventive dental visits to only patients with diabetes, smokers, or those classified as “high risk” by their genetic test.<sup>1</sup> They further claimed that the study also supported a different IL-1 test (the “PerioPredict” genetic test) that is currently being used to determine reimbursement for levels of preventive care by one major insurer.

A recent review of clinical studies<sup>2</sup> showed that independent reanalyses led to changes in findings and conclusions different from those of the original studies over one-third of the time. Unfortunately, independent reanalyses are rarely carried out on the data reported in published studies. This raises concern that the scientific community and the general public may be accepting findings that are of questionable validity. Large studies, such as the tooth extraction study mentioned above, are time-consuming and costly, thus are unlikely

## ABSTRACT

**Background.** It has been proposed that the PST and PerioPredict genetic tests that are based on polymorphisms in interleukin 1 (IL-1) genes identify a subset of patients who experience fewer tooth extractions if provided with 2 annual preventive visits. Economic analyses indicate rationing preventive care to only “high-risk” genotypes, smokers, patients with diabetes, or combinations of these risk factors would reduce the cost of dental care by \$4.8 billion annually in the United States.

**Methods.** Data presented in the study that claimed clinical utility for the PST and PerioPredict tests were obtained for reanalysis using logistic regression to assess whether the PST genetic test, smoking, diabetes, or number of preventive visits were risk factors for tooth extraction during a span of 16 years. Consistency of risk classification by the PST (version 1) and PerioPredict (version 2) genetic tests was evaluated in different ethnic groups from the 1000 Genomes database.

**Results.** Multivariate analyses revealed association of tooth extraction with diabetes ( $P < .0001$ ), smoking ( $P < .0001$ ), and number of preventive visits ( $P = .004$ ), but no support for the PST genetic test ( $P = .96$ ) nor indication that the benefit of 2 preventive visits was affected by this genetic test ( $P = .58$ ). Classification of risk was highly inconsistent between the PST (version 1) and PerioPredict (version 2) genetic tests.

**Conclusions.** Two annual preventive visits were supported as beneficial for all patients, and there was no evidence that the IL-1 PST genetic test has any effect on tooth extraction risk or influences the benefits of 2 annual preventive visits.

**Practical Implications.** Neither IL-1 PST nor PerioPredict genetic tests are useful for rationing preventive dental care. Further research is needed to identify genetic biomarkers with robust clinical validity and clinical utility to effectively personalize the practice of dentistry.

**Key Words.** Genetic screening; genetic test; biomarker; single nucleotide polymorphism; personalized medicine; tooth extraction; tooth loss; preventive care; clinical data reanalysis.

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to be replicated. Therefore, it is essential that complete data be made available for independent reanalysis to increase assurance of the validity of study conclusions.<sup>3</sup>

Data in the original article on risk factors for tooth extraction and patient stratification were insufficient to perform an independent reanalysis.<sup>1</sup> Specifically, patients who have diabetes and/or were smokers—2 well-established risk factors for tooth loss—were pooled together within “high-risk groups” that also included patients who were classified as “high risk” based solely on their PST genotype test. Consequently, it was not possible to evaluate whether the PST genetic test itself had any effect on the clinical outcomes independent of smoking and/or diabetes. In addition to the PST test (based on 1 polymorphism in the *IL1A* gene and 1 in the *IL1B* gene), the original article also introduced a new genetic test, PerioPredict (that the authors called version 2) based on 4 other polymorphisms all located in the *IL1B* gene region. It was claimed that the PerioPredict test was equivalent for clinical purposes to its predecessor, the PST genetic test.<sup>1</sup>

Although the individual single nucleotide polymorphisms (SNPs) for the new PerioPredict genetic test were reported, the way by which the genotype data from the 4 SNPs were used to classify patients into “high-risk” versus “low-risk” groups was not presented in the published study.<sup>1</sup> To perform an independent reanalysis of this study, we requested this information from the authors. We obtained data on tooth extraction outcomes separately by participants’ smoking, diabetes, PST genotype risk group, and number of preventive visits (W.V. Giannobile, DDS, DMSc, e-mail communication, December 2013). Patient age, race, or sex was not disclosed to us so these demographic measures could not be included as covariates in our reanalysis. To our knowledge, data on patients’ oral hygiene, numbers of teeth present, caries, or restorations at the start of the study period were neither obtained directly from the participants under the original study protocol nor available in the insurance database of dental procedures. In addition, the algorithm by which the 4 *IL1B* region SNPs were used to classify patients as “high risk” versus “low risk” for the PerioPredict test was also shared (W.V. Giannobile, DDS, DMSc, e-mail communication, February 2014).

In reviewing the analyses performed in the original article based on insurance claims,<sup>1</sup> we noted a number of potential problems and omissions of critical statistical tests needed to support the stated conclusions. As noted above, smoking and diabetes were confounded with potential effects of the IL-1 PST genetic test. Most important, although the authors claimed that “Interactions of risk status and frequency of preventive visits on tooth loss were evident ...” they did not actually report results of any interaction tests.<sup>1</sup> In fact, there was not even any direct evaluation of whether the PST genetic test had any effect at all on risk of undergoing tooth extraction (that is, whether

or not it was a “main effect”). Furthermore, no direct evaluation of whether the PST genetic test classifies individual patients as “high risk” or “low risk,” consistent with how the PerioPredict genetic test classifies the same patients, was presented. A figure in the appendix of the published study<sup>1</sup> showed comparisons of the percentage of patients with tooth loss events for “low-risk” versus “high-risk” groups and the authors of the study concluded that their version 2 (PerioPredict) test “gave results comparable with those in version 1 relative to differences between 1 and 2 preventive visits.” However, the “high-risk” group presented in their figure confounded patients who are classified as “high risk” solely because of their PST or PerioPredict genetic tests with other patients who were “high risk” because they have diabetes or were smokers. Furthermore, only group frequencies were presented in the figure and there was no way of knowing if individual patients were consistently classified as “low risk” or “high risk,” or may change their risk classification depending on which test is used.

There is great potential for advances in genomics to expand our knowledge of oral disease etiology and to improve patient care through personalized approaches to diagnosis, treatment, and prevention of oral and dental diseases. However, it is essential that these powerful strategies are supported by objective and independent assessment of robust clinical data free from conflict of interest.<sup>4</sup> Implementation of patient stratification for preventive dental care based on the IL-1 PerioPredict genetic test carries significant implications for the standard of care in dentistry. Therefore, it is essential that the data from clinical studies such as this be available for independent reanalyses.

The purpose of our study was to conduct a reanalysis of data provided by the authors of the published review of dental benefits claims and discuss why our findings lead to very different conclusions.

## METHODS

Using only the data presented in the published study of *IL1A/IL1B* genotypes and tooth extractions,<sup>1</sup> it was not possible to reanalyze the authors’ most important conclusion that an interaction exists between the PST genetic test and number of preventive visits. We obtained from W.V. Giannobile, DDS, DMSc (e-mail communication, December 2013) the numbers of participants with 1 versus 2 annual preventive visits and the

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**ABBREVIATION KEY.** ASW: African Americans from the Southwest. CEU: Caucasians from Utah. CHB: Han Chinese from Beijing. FCGR: Fc fragment of IgG, low affinity Ila or IIb, receptor. HLA: Human leukocyte antigen. IL-1: Interleukin 1. LTF: Lactotransferrin. PUR: Puerto Ricans. SNPs: Single nucleotide polymorphisms. TLR: Toll-like receptor. TNF: Tumor necrosis factor. VDR: Vitamin D receptor.

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