

# 1 Study of a Relative Polygenic Risk Score Assay for Common Oral 2 Health Conditions

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## 11 Abstract

12 This single center observational study measured a relative polygenic risk score for two oral health  
13 conditions from 27 dental patients. Calculating an individual's polygenic risk score is an emerging  
14 tool in genetics. Its potential to focus on preventative healthcare in populations has allowed it to be  
15 implemented by health systems like the UK's National Health Services (Genome UK). There are  
16 several oral health conditions that have a genetic basis including dental caries and periodontal  
17 disease. Despite good oral hygiene habits, some individuals may have an increased genetic  
18 predisposition to certain dental problems. The Canadian Dental Association reported that an  
19 estimated 2.26 million school-days are missed each year due to dental-related illness and tooth decay  
20 accounts for one-third of all day surgeries performed on children between the ages of 1 and 5. In the  
21 United States, a child is five times more likely to seek emergency room treatment for dental problems  
22 than for asthma, often because they are unable to see a dentist, are uninsured or cannot afford routine  
23 dental care. Upon review of the literature, we identified common genetic variants with evidence for  
24 association with periodontal disease and dental caries and developed a genotyping panel coupled with  
25 a relative polygenic risk score. We assessed the performance of this assay in a cohort of 27 dental  
26 clinic patients by running polygenic risk scores against a baseline derived from the publicly available  
27 1000 Genomes Project dataset as a reference population. The baseline score distribution was used to  
28 define categories of relative risk. Evaluation of the relative-polygenic risk score in larger case control  
29 cohorts should be considered to weigh the utility of the proposed relative risk scoring model;  
30 allowing for the stratification of patients who may benefit from enhanced monitoring or proactive  
31 oral health care regimens at the discretion of dental healthcare providers.

## 32 1 Introduction

33 It is well established that many diseases and conditions have an underlying genetic component,  
34 however, determination of genetic etiology can be challenging especially for multifactorial diseases  
35 (Dudbridge, 2016; Chasioti et al., 2019). Multifactorial, or complex diseases, arise from a  
36 combination of genetic predisposition and extrinsic factors such as environmental exposures or  
37 lifestyle choices. Unlike Mendelian (monogenic) disorders where variation in a single gene can give

38 rise to a particular phenotype, multifactorial (polygenic) disorders are often influenced by many  
39 genes, each of small effect (Manolio et al., 2009; Golan et al., 2014; Chasioti et al., 2019; Cano-  
40 Gamez and Trynka, 2020). The development of polygenic risk scores enables a deeper understanding  
41 of the impact genetics has on the development of diseases and conditions (Torkamani et al., 2018;  
42 Chasioti et al., 2019; Klarin and Natarajan, 2022). A polygenic risk score (PRS) illustrates how an  
43 individual's risk of developing a disease or condition compares to the broader population baseline. A  
44 PRS is comprised of genetic variants that have been identified to be associated with a particular  
45 disease or condition, typically as a result of large Genome-Wide Association Studies (GWAS) (Choi  
46 et al., 2021). Using statistical models and scoring algorithms, it is possible to evaluate how an  
47 individual's unique genetic profile contributes to their overall risk for a disease or condition of  
48 interest (Dudbridge, 2013; Chang et al., 2015; Choi et al., 2021).

49 PRS is an emerging tool in genetics. Its potential to focus on preventative healthcare in populations  
50 has allowed it to be implemented by health systems such as the UK's National Health Services  
51 (Genome UK). PRS for common diseases like coronary artery disease and type 2 diabetes have been  
52 developed and analyzed (Khera et al., 2018). Despite good oral hygiene habits, some individuals may  
53 have an increased genetic predisposition to certain dental problems. There are several oral health  
54 conditions that have a genetic basis including periodontal disease, dental caries (cavities) resistance,  
55 and oral cancers (Michalowicz et al., 2000; Bretz et al., 2005; Sarode et al., 2018; Shungin et al.,  
56 2019). Two of these conditions, periodontitis and dental caries, were estimated to be the eleventh and  
57 first most prevalent diseases respectively in a global study (Vos et al., 2017). Global economic  
58 impact of dental diseases amounted to \$442 billion USD in 2010 (Listl et al., 2015).

59 Periodontal disease (PD) is a chronic inflammatory disease that leads to the degradation of tooth-  
60 supporting structures (Shungin et al., 2019). At first a patient might present with gingivitis, which is  
61 characterized by swollen and red gums that tend to bleed. Gingivitis can progress to periodontitis,  
62 which can result in bone or tooth loss as the gum detaches from the tooth (Kinane et al., 2017). It has  
63 been found that PD may increase the risk of cardiovascular disease by 19%. In addition, Type 2  
64 diabetic individuals with severe PD have three times greater mortality risk compared to those with no  
65 or mild periodontitis. Periodontal therapy has also been shown to improve glycemic control in type 2  
66 diabetic individuals (Nazir, 2017). PD is the main cause of tooth loss and is one of the most common  
67 oral conditions in the human population (Nazir, 2017; Vos et al., 2017).

68 Tooth decay results from destruction of the tooth's enamel. Tooth decay can be caused by the acid  
69 produced by the bacteria responsible for breaking down food in the mouth. The acid-induced enamel  
70 erosion creates a hole (cavity) in the tooth. If left untreated, infection or more severe outcomes such  
71 as tooth loss can occur (National Institute of Dental and Craniofacial Research, 2019). Worldwide,  
72 more than two billion people have cavities of the permanent teeth, and 520 million children have  
73 cavities in their primary teeth (Vos et al., 2017). There has been an increase in prevalence in  
74 developing countries due to the growing consumption of sugary foods, poor tooth brushing habits,  
75 and absence of adequate dental services (Teshome et al., 2021).

76

77 Oral disease prevention strategies should be incorporated in chronic systemic disease preventative  
78 initiatives to lessen the burden of disease in the population. Mitigating the incidence and prevalence  
79 of PD can reduce its associated systemic diseases (Liccardo et al., 2019). Overall improvements in  
80 oral health may lead to significant economic benefit with respect to decreased cost of treatment and  
81 labour resource allocation in dental clinics (Listl et al., 2015). Based on the existing literature, we

82 identified common genetic variants with evidence for association with PD and tooth decay/cavities  
83 and developed a genotyping panel coupled with a relative polygenic risk score. In this study we  
84 assessed the performance of the assay in a cohort of 27 dental clinic patients. A genotyping panel that  
85 integrates a relative-polygenic risk score can be utilized by dental professionals to identify  
86 individuals' genetic contribution to the overall predisposition to common oral health conditions.

## 87 **2 Materials and Methods**

### 88 **2.1 Patient Enrolment**

89 Participants were required to be 18 years old or older for inclusion in this study. Participant selection  
90 occurred independent of sex, ethnicity, and of any diagnosis or epidemiological indices. Informed  
91 consent was obtained from each of the 29 participants. The cohort consisted of 11 males, 15 females,  
92 and 3 individuals whose biological sex was not reported. Participants ranged in age from 21-87 years  
93 old. Enrolment took place over the course of one day (December 11th, 2021).

### 94 **2.2 Study Design**

95 Participant recruitment occurred at a single site (private dental office) in Ontario, Canada. The study  
96 was designed as a cohort study whereby individuals were approached during routine practice, under  
97 the dental clinic's natural settings. Written informed consent was obtained from study participants.  
98 Consented participants provided a buccal (cheek) swab for genetic testing. Select demographic  
99 information including biological sex and age was recorded. Genetic data was deidentified. Individual  
100 genetic testing reports were generated based on genetic variants associated with the two oral health  
101 indications (periodontal disease and cavities/tooth decay). Reports were issued to the study  
102 investigator and unblinded for the dental healthcare provider for discussion at a subsequent regularly  
103 scheduled visit. The study protocol was reviewed and approved by an independent ethics review  
104 board.

### 105 **2.3 Variant Selection/Panel Design**

106 Genetic variants to be included in an oral health-based genetic panel were first identified following a  
107 thorough review of the literature encompassing genetic risk and susceptibility for PD and dental  
108 cavities/tooth decay. Risk-associated variants were selected from a combination of case-control,  
109 meta-analyses, and GWAS publications. The list of candidate variants was narrowed down by  
110 considering study design/phenotype criteria, statistical significance, availability of effect alleles and  
111 weights in the original publications, and availability of coordinates in the Genome Reference  
112 Consortium Human GRCh38.p13 (GRCh38) reference genome assembly. After quality control (QC),  
113 a total of 25 single nucleotide polymorphisms (SNPs) were selected for PD, and 35 SNPs for  
114 cavities/tooth decay. These SNPs were included in the design of the proprietary Oral Health Panel for  
115 downstream application with the Agena Bioscience MassARRAY® System with Chip Prep Module  
116 (CPM) 96 (CP1603036).

### 117 **2.4 Relative-Polygenic Risk Score (R-PRS) Development**

118 The candidate SNPs were subsequently evaluated for utility in the development of a PRS in a  
119 background (baseline) control population. The 1000 Genomes Project (1000G) reference data set was  
120 selected as the control cohort for this purpose. The 1000G cohort consists of genetic data from over  
121 2500 consented subjects from 26 global populations (Auton et al., 2015). The distribution of risk  
122 scores obtained from the control cohort thus served as the baseline against which all subsequent

123 genotyping results can be compared to, enabling the derivation of an individual's polygenic risk  
 124 score relative to the general population, referred to as the relative polygenic risk score (R-PRS). An  
 125 assessment of specificity and sensitivity was not performed as the intent of the relative polygenic risk  
 126 score outlined herein is to discern where an individual's risk score lies with respect to the distribution  
 127 observed in a population of self-reported healthy individuals.

128 A subset of candidate variants was selected for inclusion in the construction of the R-PRS based on  
 129 the following criteria: (1) presence of the SNP in the 1000 Genomes Phase 3 Integrated Variant Calls  
 130 dataset and (2) presence of effect (risk) alleles in either the reference or the alternative allele in the  
 131 1000 Genomes dataset. A separate R-PRS baseline was constructed for each oral health condition.  
 132 Bioinformatic processing was achieved using PLINK 1.9, an open-source whole genome association  
 133 analysis toolkit (Purcell et al., 2007). Development of each R-PRS followed a clumping and  
 134 thresholding approach adapted from Choi et al. (Choi et al., 2021). The subset of SNPs that passed  
 135 QC criteria were used in the final risk score calculations to establish the baseline distribution. Score  
 136 calculation followed an additive model, whereby the SNP effect size (logarithm of the reported odds  
 137 ratio),  $S_i$ , was multiplied by the dosage (copies of the effect allele),  $G_{ij}$ , and summed across all SNPs.  
 138 To account for missing genotypes, the sum is divided by the number of non-missing SNPs,  $M_j$ ,  
 139 multiplied by the ploidy,  $P$ .

$$140 \quad PRS_j = (\sum_i^N S_i * G_{ij}) / (P * M_j)$$

141 Where  $G_{ij}$  is the genotype for the  $i^{\text{th}}$  individual and  $j^{\text{th}}$  SNP

142 Risk scores for each of the 1000G subjects were plotted on a curve and the data assessed for  
 143 normality for each condition tested. The risk score distributions were divided into percentiles,  
 144 corresponding to categories of relative risk. These categories were used to assign relative risk to the  
 145 participants of the study based on their personal risk scores.

## 146 **2.5 Genotyping and Quality Control**

147 Buccal swabs were obtained from 29 subjects using the ORAcollect•DNA (OCR-100) kit (DNA  
 148 Genotek). Genomic DNA was extracted using the prepIT®•L2P protocol for 0.5mL of sample (DNA  
 149 Genotek). Quantity and purity of DNA was determined using absorbance at wavelengths of 260 and  
 150 280nm (NanoDrop™ One, Thermo Scientific™). Sample identification and authentication was  
 151 performed using the iPLEX® Pro Sample ID Panel (Agena Bioscience). The Sample ID Panel is  
 152 comprised of 44 SNPs that are used to generate a unique genetic fingerprint for each sample, in  
 153 addition to three biological sex markers and five copy number quality markers. This panel also serves  
 154 as a secondary metric for DNA quality assessment. Samples are flagged as QC failures if any of the  
 155 following criteria are met: (i) gender mismatch identified (discrepancy between detected and reported  
 156 gender), (ii)  $\geq 14$  unsuccessful SNP calls, (iii)  $>11$  low quality calls, (iv)  $\leq 500$  amplifiable copies of  
 157 DNA, or (v) an unexpected match between two presumably unrelated patient samples. Samples that  
 158 passed QC were prepared for genotyping with the oral health panel and QC failures were re-  
 159 processed.

160 Forward and reverse primers targeting the candidate SNPs were designed in multiplex by Agena  
 161 Bioscience for the Oral Health Panel. A total of 2  $\mu$ l of genomic DNA (20 ng/ $\mu$ l concentration) was  
 162 loaded in 96 well PCR plates along with the PCR master mix. The PCR amplification steps were  
 163 performed on the T100 Thermal Cycler (Bio-Rad). Post-PCR processing with shrimp alkaline  
 164 phosphatase (SAP), single base extension reactions, and SNP genotyping was performed as per the

165 manufacturer's protocol for custom MassARRAY® panels using iPLEX Pro chemistry (Agena  
 166 Bioscience). The 29 samples were genotyped in two separate batches. A subset (n=3) of DNA  
 167 samples were randomly selected to test inter-run reproducibility. Three non-template, negative  
 168 controls were loaded onto each plate. Biological samples were flagged as QC failures if the high-  
 169 quality genotype call rate was  $\leq 80\%$ . Samples failing QC criteria were not assigned an R-PRS.

## 170 **3 Results**

### 171 **3.1 Oral Health Panel PRS Show Normal Population Distribution**

172 The original genotyping panel design included 25 and 35 SNPs for PD and cavities/tooth decay  
 173 respectively. These SNPs were selected on the basis of having published evidence for statistically  
 174 significant disease association and coordinates in the GRCh38 reference genome assembly. Summary  
 175 statistics were obtained from the corresponding publications for downstream application in the  
 176 development of the PRS algorithm.

177 PRS analyses and baseline scoring was performed with PLINK 1.9, using the publicly available  
 178 1000G dataset as a reference population baseline (Purcell et al., 2007; Chang et al., 2015; Fairley et  
 179 al., 2020). The baseline data (summary statistics) was first subjected to QC, whereby SNPs with two  
 180 or more alleles or ambiguous alleles were removed. For the target data (1000G cohort data), SNPs  
 181 were removed if (i) the minor allele frequency is  $<0.01$ , (ii) Hardy-Weinberg equilibrium is  $<1E-6$ , or  
 182 (iii) if the SNP exhibited a rate of missingness  $>0.01$  in the 1000G cohort. Additional QC filters were  
 183 applied to remove samples with a high rate of genotype miss-calls, sex discordance, or close  
 184 biological relatedness. After performing QC, 11 PD-associated SNPs and 8 cavities-associated SNPs  
 185 were removed from the PRS algorithm. A total of 2548 and 1863 subjects were retained for PD and  
 186 cavities respectively. Next, clumping was performed to remove SNPs if the  $r^2$  linkage disequilibrium  
 187 threshold is  $>0.1$  with the index SNP. After clumping, 11 SNPs for PD and 27 SNPs for cavities  
 188 remained for baseline scoring. The oral health conditions were scored separately using the additive  
 189 dosage weighted model (Choi et al., 2021).

190 The resulting distribution of polygenic risk scores was approximately normally distributed (Figures  
 191 1, 2). PD showed stronger evidence of normality with points following a nearly linear line while  
 192 cavities showed a poorer fit with skewing towards its low and high ranges. (Figures 1 and 2 in  
 193 Supplementary Material). The median polygenic risk score was 0.1462235 for PD and -0.00203701  
 194 for cavities. The risk categories were calculated based on the 5<sup>th</sup>, 15<sup>th</sup>, 50<sup>th</sup>, 85<sup>th</sup>, and 95<sup>th</sup> percentiles  
 195 as the cut-offs for low, intermediate-low, average, intermediate-high, and high-risk categories  
 196 respectively (Figures 3, 4, and Table 1 in Supplementary Material). The risk categories observed in  
 197 the control cohort thus serve as the baseline against which an individual's risk can be assessed. All  
 198 subsequent individual risk assessment is hence relative to that of the general population.

### 199 **3.2 Independent Cohort Exhibits Normal Distribution**

200 An assessment of the MassARRAY genotyping call rate revealed four underperforming SNP assays  
 201 across the cohort. These SNPs had significant low quality or missing genotype calls and/or  
 202 indistinguishable genotype call clusters. These SNPs are to be removed from the PRS algorithm and  
 203 the 1000G baseline moving forward. The assessment of inter-run reproducibility revealed a mean  
 204 genotype call concordance rate of 98% across the three tested samples. A total of 27 out of 29 DNA  
 205 samples passed QC, with a 93.5% mean high quality call rate, and were assigned an R-PRS.

206 Relative risk scores were calculated for each subject using the same approach as the 1000G control  
207 cohort such that each individual score could be placed in the context of the baseline distribution. The  
208 poor performing SNPs were labelled as missing genotypes and accounted for in the PRS calculation  
209 using the conservative substitute formula ( $2 * \text{minor allele frequency} * \text{effect size}$ ), enabling a  
210 direct comparison to the baseline risk scores. The distribution of risk scores observed in the study  
211 cohort closely followed the distributions of the 1000G cohort for both conditions. The quantile plots  
212 exhibited data normality (Figures 3 and 4 in Supplementary Material). As expected, most relative risk  
213 scores fell in the 50<sup>th</sup> percentile (average relative risk) for both conditions (Figure 5). One high risk  
214 categorization was obtained for each condition. Despite the small sample size, this preliminary  
215 evaluation of the distribution of risk scores and relative risk categorizations suggest that the SNPs  
216 included in the final PRS algorithm can effectively stratify individuals into distinct relative risk bins.

## 217 4 Discussion

218 The availability of GWAS data has made it possible to better understand and model genetic  
219 susceptibility for polygenic diseases and traits such as PD and cavities (Chasioti et al., 2019; Lambert  
220 et al., 2019; Shungin et al., 2019). Through the curation of disease-associated SNPs and development  
221 of PRS algorithms in a large, ethnically diverse control population, we demonstrated an approach that  
222 can be used to infer relative genetic risk for two common oral health conditions. The results of this  
223 study demonstrate the utility of an oral health genotyping panel coupled with a relative-PRS to  
224 stratify patients into one of five categories of genetic risk relative to that of the general population.  
225

226 One of the most challenging aspects of PRS is ensuring that the generated scores are equally  
227 applicable across all ethnic groups. Most existing data available within genome wide association  
228 studies are from individuals of European ancestry, as a result the current scores are most predictive  
229 for individuals within this population (Duncan et al., 2019; Lewis and Vassos, 2020). This issue  
230 needs to be highlighted as minority ethnic groups may be under-represented in research studies. This  
231 may possibly lead to a less predictive score for the under-represented ethnic groups (Lewis and  
232 Vassos, 2020). We (and others) within this space are addressing this gap as we continuously grow  
233 and diversify our population database (Morales et al., 2018). By doing so, our algorithm will in  
234 parallel be continuously updated to provide increasingly more accurate relative polygenic risk scores.  
235 We also acknowledge that our study lacked the incorporation of individuals' clinical background,  
236 which was beyond the scope of the study. We are currently building our algorithm to include the  
237 effects of environmental and behavioral factors to better estimate individual risk. Future work will be  
238 centered on evaluating the sensitivity and specificity of the proposed risk scoring algorithm. These  
239 metrics can be used to assess the ability of the risk score to reliably stratify patients who are high risk  
240 for the two dental conditions tested. While this assessment could not be performed in the current  
241 analysis, the approach outlined provides a means to contextualize the effect of risk associated SNPs  
242 across individuals in the absence of an independent validation cohort of sufficient sample size.  
243

244 The need for genetic curriculum and education has been raised in the dental community in order to  
245 better understand how genetic testing can benefit patient care (Behnke and Hassell, 2004; Hart and  
246 Hart, 2016). It will be important to engage with the dental community and other healthcare providers  
247 to equip them with the knowledge needed to make informed decisions based on the outcomes of  
248 genetic testing, whether it be for Mendelian diseases or multifactorial conditions (Zimani et al.,  
249 2021). The results of the relative-PRS assessment can be used at the discretion of dentists to identify  
250 patients that might benefit from enhanced surveillance. It will be important to weigh the genetic risk  
251 in the context of other clinical and lifestyle factors that play a role in these multifactorial conditions.  
252 While the R-PRS is not intended to be diagnostic, it offers a more comprehensive insight to the

253 personal genetic susceptibility for PD and cavities that cannot be gained from a report on singular  
254 risk variants at common polymorphic loci. Extensive testing and validation will be an essential  
255 prerequisite to adoption of polygenic risk scoring models in the clinic.

256 **5 Conflict of Interest**

257 SM, JG, PQ, AK, MG are shareholders in AI Genetics. SM, PQ, AK, MG, and JG are employees of  
258 AI Genetics.

259

260 **6 Author Contributions**

261 SM designed the study protocol, supported patient enrolment, and oversaw the manuscript  
262 development. PQ and AK conducted experimentation. PQ, AK, and MG drafted the manuscript. SG  
263 provided clinical access and subject expertise. JG provided subject expertise and oversight. All  
264 authors contributed to manuscript review and editing.

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269 Author 1: Contributed to conception, design, data acquisition and critically revised the manuscript.

270 Author 2: Contributed to data acquisition and critically revised the manuscript.

271 Author 3: Contributed to conception, design, data acquisition and interpretation, drafted and critically  
272 revised the manuscript.

273 Author 4: Contributed to conception, design, data acquisition and interpretations, performed  
274 statistical analyses, drafted and critically reviewed the manuscript.

275 Author 5: Performed statistical analyses, drafted and critically revised the manuscript.

276 Author 6: Contributed to conception, design and critically revised the manuscript.

277 **9 Supplementary Material**

278 The Supplementary Material for this article can be found online at:

279 **10 Data Availability Statement**

280 Further inquiries regarding generated datasets can be directed to the corresponding author.

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366 **Figure 1** PRS distribution for periodontal disease in the reference population (n=2548) calculated  
367 using PLINK 1.9 PRS pipeline.

368 **Figure 2** PRS distribution for cavities in the reference population (n=1863) calculated using PLINK  
369 1.9 PRS pipeline.

370 **Figure 3** Risk score bins derived from the reference population used to define relative risk categories  
371 for cavities.

372 **Figure 4** Risk score bins derived from the reference population used to define relative risk categories  
373 for periodontal disease.

374 **Figure 5.** Distribution of relative risk categorizations associated with polygenic risk scores observed  
375 in the study cohort (n=27). **(A)** Cavities distribution. **(B)** Periodontal disease distribution.

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