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Genetic polymorphisms in TNF-α as a potential biomarker for oral health-related quality of life in children

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Abstract: This cross-sectional study aimed to assess if genetic polymorphisms in *TNF*-α are associated with a negative impact on Oral Health-Related Quality of Life (OHRQoL) in children with dental caries. A total of 307 pairs of parents/caregivers and children aged two to five years were selected. The children were clinically evaluated and classified according to caries experience and severity of active caries. The Brazilian Portuguese version of the Early Childhood Oral Health Impact Scale (ECOHIS) was used to assess OHRQoL. Genotyping analysis of genetic polymorphisms in *TNF*-α (rs1799724, rs1799964, and rs1800629) was performed using real-time polymerase chain reaction. In the recessive model, children with the CC genotype of *TNF*-α (rs1799964) had a significantly high chance of poor OHRQoL in the symptom domain (pain), in both the caries experience (p = 0.045) and the high-severity active caries phenotypes (p = 0.033) (Mann-Whitney U test). It was concluded that genetic polymorphisms in *TNF*-α are associated with OHRQoL related to the symptom domain (pain), suggesting that *TNF*-α could be used as a potential biomarker for OHRQoL. Understanding the genetic aspects associated with OHRQoL will allow the early identification of patients with OHRQoL disparities and provide personalized healthcare.

Keywords: Genetics; Dental caries; Oral Health; Quality of Life.

Introduction

Quality of life is the individual's perception of their position in life, in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns.[1] Quality of life indicators assess general health-related quality of life (HRQoL) and include a variety of functional changes and disabilities that can afflict people.[2] In dentistry, oral health-related quality of life (OHRQoL) is a multidimensional construct that reflects, among other things, the individual's comfort when eating, during sleep, social interactions, self-esteem, and satisfaction with their oral health. Questionnaires designed to assess the impact of oral problems on the quality of life are specific instruments generically called sociodental indicators.[3]

Some health studies in medicine have demonstrated that genetic polymorphisms affect HRQoL.[4-6] The Genetics and Quality of Life

Research (GeneQoL) Consortium lists several genes associated with HRQoL, affecting symptoms such as pain, mood, and fatigue. These symptoms may affect social functioning indirectly; however, there could be direct connection between the biological variables and the ability to perform social behaviors.[7] Among the candidate genes suggested by the GeneQoL Consortium study, tumor necrosis factor α *(TNF-a*) was associated with HRQoL symptoms related to general health, such as pain, mood, and fatigue.[7] TNF-a is a pleiotropic cytokine produced by many different types of cells in the body; it regulates a number of critical functions, including cell proliferation, survival, differentiation, and apoptosis.[5] There is emerging evidence regarding the association between TNF-a and HRQoL.[4,7,8-14]

Dental caries has high prevalence as a clinical indicator and has a strong impact on OHRQoL[15] as a sociodental indicator in preschool children.[16] Untreated dental caries and its clinical consequences have a negative impact on OHRQoL of schoolchildren[17,18] leading to functional limitations, influencing the psychological aspects, family, and social relationships.[16] Dental caries is a complex condition that involves clinical and sociodental indicators.[16] The understanding of OHRQoL in dental caries is very important, as it combines the information from sociodental indicators with those from clinical indicators. Sociodental indicators measure social and psychological parameters of oral health.[16,19]

Regarding oral conditions, the influence of genetic polymorphisms on OHRQoL in patients requiring orthognathic surgery was the first insight into this association.[20,21] Therefore, new insights regarding the effect of genetic variations on OHRQoL are necessary to identify possible biomarkers in dentistry. This study aimed to investigate whether genetic polymorphisms in *TNF*-α are associated with OHRQoL in children with dental caries.

Methodology

This cross-sectional study was performed following the checklist provided by the Strengthening the Reporting of Genetic Association Studies (STREGA) statement.[22] The Declaration of Helsinki guidelines were applied and ethical approval was obtained from the local human ethics committee (#68539/#60156). The parents/caregivers of all children signed a written informed consent form, allowing the child to participate in the study.

Sample selection

The study participants consisted of pairs of parents/caregivers and children aged two to five years who were recruited for convenience from 33 public schools in the city of Nova Friburgo, State of Rio de Janeiro, in the southeast region of Brazil, over a period of 18 months. The exclusion criteria were parents/caregivers who did not write or speak fluent Brazilian Portuguese, parents/caregivers who did not sign or return the informed consent form, or did not properly fill out the questionnaires. Children with mixed dentition, who did not allow the exams to be completed or with other potential confounding factors affecting the OHRQoL (*i.e.*, malocclusion such as increased overjet, anterior open bite, posterior crossbite, and anterior crossbite; dental trauma such as fractures, avulsion, and tooth discoloration; children undergoing orthodontic or prosthetic treatment; syndromic; or with special needs) were also excluded.

Non-clinical data assessment

Parents/caregivers answered a questionnaire regarding their children's characteristics (sex, ethnicity, and age). The sociodental indicator used was the Early Childhood Oral Health Impact Scale (ECOHIS), validated in the Brazilian Portuguese language.[23] All parents were requested to complete the questionnaire. They filled out the questionnaires at home, returned them, along with the signed informed consent to the school.

The ECOHIS consists of 13 items corresponding to four descriptive domains in the child subscale: child symptoms domain (one item), child function domain (four items), child psychological domain (two items), and child self-image/social interaction domain (two items), and two domains for the family subscale: parent distress domain (two items) and family function domain (two items). This scale evaluates parents' perceptions of their children's OHRQoL. The response categories of the ECOHIS were coded on a five-point

scale: 0 = never, 1 = hardly ever, 2 = occasionally, 3 = often, and 4 = very often. The total ECOHIS score and scores for the individual domains were calculated as a simple sum of the response codes. This scale ranges from 0 to 52 (0–36 for the child subscale and 0–16 for the family subscale). Only the child subscale was used for comparison with *TNF*-α genetic polymorphisms.

Before starting the study, a small pilot study was conducted to detect the reliability of the OHRQoL questionnaire in the target population. A new convenience sample (not part of the study population) of parents/caregivers and their children was recruited (n = 34). The test-retest reliability analysis requires individuals' conditions to remain the same between the two administrations of the questionnaire. Therefore, the second questionnaire was administered two weeks later. The intraclass correlation coefficient (0.98) was excellent.

Clinical data assessment

Two specialists in pediatric dentistry (LAAA and LHMP), previously trained and calibrated, performed the children's oral examinations at school. The training exercise (a total of 24 h over 1 week) for dental caries diagnosis was performed using images from different clinical situations. Reliability was assessed using weighted (dental caries) kappa statistics for two separate dental examinations. This was performed in 30 children aged two to five years (not part of the study population) with a 1-week interval between sessions. Inter- and intra-examiner reliability presented substantial to almost perfect agreement (κ = 0.80 and 1.00, respectively) according to Cohen.[24]

The examination was conducted at school with children seated in a chair using natural light, tongue depressors, and gauze. Oral hygiene was performed with previous tooth brushing to remove biofilms. The dental caries index recommended by the World Health Organization for oral health surveys was used.[25] Information on the decayed, missing, and filled teeth index (dmf-t index) was obtained. White spot lesion was also evaluated according to '*the first sign of caries lesion on enamel that can be detected with the naked eye*' and used alongside with terms '*initial*' or '*incipient*' lesions.[26]

Biological material collection and molecular analysis

Genomic DNA for genotyping analysis was extracted from buccal cells using a previously reported method.[27] The genotyping analysis was performed only in children with dental caries experience (white spot lesion ≥ 1 and/or dmf-t ≥ 1) and in children with high-severity active caries cases (component d ≥ 5). The amount and purity of DNA were determined using a spectrophotometer (Nanodrop 1000, Thermo Scientific, Wilmington, NC, USA). Only DNA samples with an A260 nm/A280 nm ratio of 1.8 or higher were used.

According to the STREGA statement, items 2 and 3 highlight the importance of a scientific basis and the justification of the investigation.[22] *TNF*-α was chosen for this study because of its previous association with HRQoL, as well as the fact that TNF-α was associated with quality of life symptoms related to general health as pain, mood, and fatigue by the GeneQoL Consortium.[7] We used the University of California Santa Cruz (UCSC) Genome Browser website to identify previously characterized single nucleotide polymorphisms for each candidate gene (Table 1), according to their possible function regulation. Upstream transcript variants [rs1799964 (C > T), rs1799724 (C > T), and rs1800629 (rs1800629 (A > G)] were genotyped using TaqMan genotyping assay and Agilent Technologies QPCR System (Stratagene Mx3005P). Assays and reagents were supplied by Applied Biosystems (Foster City, USA). All examiners at the laboratory were blinded to the sample group assignment.

Statistical analysis

Data were analyzed using IBM Statistical Package for Social Science, v.23.0 (IBM, Armonk, USA), with a significance level of $p < 0.05$. The variables were tested for a normal distribution. The numerical variables did not present a normal distribution and are represented as medians. OHRQoL analysis was dichotomized by the impact median value and values above the median were considered to have a high negative impact on OHRQoL and those below the median to have a low negative impact on OHRQoL. The association between the variables was

Table 1. Studied genetic polymorphisms in *TNF*-α.

rs#	Position	Gene consequence	Ref SNP alleles	MAF
rs1799724	chr6:31574705 (GRCh38.p12)	2KB Upstream Variant	C/T	T = 0.0990
rs1799964	chr6:31574531 (GRCh38.p12)	2KB Upstream Variant	C/T	C = 0.2190
rs1800629	chr6:31575254 (GRCh38.p12)	2KB Upstream Variant	A/G	A = 0.0903

MAF: Minor allele frequency; SNP: single nucleotide polymorphisms; aA: adenine; C: cytosine; G: guanine; T: thymine. Obtained from databases: http://www.thermofisher.com, http://www.ncbi.nlm.nih.gov and http://genome.ucsc.edu

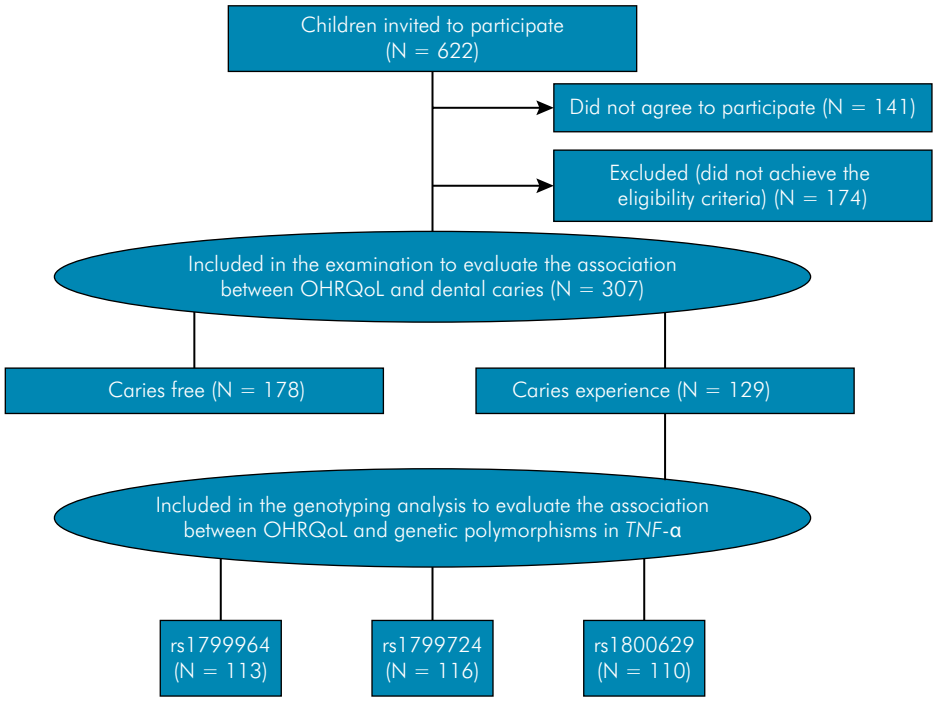

Figure 1. Sample flowchart.

assessed using bivariate Poisson logistic regression. The prevalence rate (PR) was calculated. Genotype analyses were performed in recessive and dominant models using the Mann–Whitney test. The standard chi-square test was used to test for deviation from the Hardy–Weinberg equilibrium.

Results

Initially, 622 children/caregivers were invited to participate in the study. One hundred and forty-one patients were lost. They did not agree to complete the OHRQoL questionnaire. After applying the eligibility criteria, 307 pairs of parents/caregivers and children were included. The response rate was 63.8% (481/307). A flowchart summarizing the patient selection process is presented in Figure 1.

The mean age of the children was 3.47 (SD = 1.38). Sex and ethnicity distributions were 50.8% female and 60.9% Caucasian, respectively, although these factors did not influence the outcome.

Caries experience was associated with the OHRQoL (Table 2) ($p < 0.05$). According to parents/caregivers' perceptions of OHRQoL, children with caries experience were more likely to have a higher negative impact on OHRQoL than children without caries experience ($p = 0.022$; PR 1.46, 95% CI 1.05–2.02). Regarding the subscale

domain, parents/caregivers of children with caries experience also reported a higher negative impact on OHRQoL in the function domain than children without caries experience (p = 0.009; PR 1.47, 95% CI 1.10–1.97).

The associations between *TNF*-α and OHRQoL domains in children with caries experience (n = 129) and high-severity active caries (n = 96) are presented in Table 3. In the recessive model, children with the CC genotype of *TNF*-α (rs1799964) had a significantly higher chance of poor OHRQoL in the symptom domain than those with the other genotypes, in the phenotype of caries experience (p = 0.045), and in the high-severity active caries phenotype ≥ 5 (p = 0.033).

Discussion

The impact of dental caries on OHRQoL has been studied extensively and a recent systematic review and meta-analysis reported that dental caries has a negative impact on OHRQoL.[15] Evaluation of other oral conditions, such as dental trauma and malocclusions,[28,29] has indicated that dental caries is the oral condition that presented the highest negative impact on OHRQoL in preschool children. This could be explained by the fact that dental caries is a condition that causes children to frequently miss school, as well as experience difficulty in eating certain foods, drinking hot or cold beverages, and in pronouncing some words.[16] In fact, in the present study a significant association was observed with the ECOHIS function domain.

In this study, we hypothesized that OHRQoL in patients with dental caries is influenced by individual genetic background. Only children with dental caries were included in the genetic analysis, as the main goal of the present study was to investigate the role of these genes in the OHRQoL of affected children. In medicine, HRQoL is already known to be affected by demographic characteristics (e.g., age, sex, and race), lifestyle factors (*e.g.*, diet and physical activity), and psychological factors, such as mood state and stress.[30,31] It is therefore suggested that individual

Table 2. Association between caries and OHRQoL

Oral Health-related Quality of life (OHRQoL)	Caries experience		Statistics	
	Caries free (n = 129)	Caries experience (n = 178)	p-value	PR (95%CI)
	n (%)	n (%)		
Child Subscale				
1 - High negative impact OHRQoL	31 (24.0)	66 (37.1)	0.022	1.46 (1.05-2.02)
0 - Low negative impact OHRQoL	98 (76.0)	112 (62.9)		
D1 – Symptoms				
1 - High negative impact OHRQoL	99 (76.7)	137 (77.0)	0.964	1.00(0.73 – 1.37)
0 - Low negative impact OHRQoL	30 (23.3)	41 (23.0)		
D2 – Function				
1 - High negative impact OHRQoL	41 (31.8)	84 (47.2)	0.009	1.47 (1.10-1.97)
0 - Low negative impact OHRQoL	88 (68.2)	94 (52.8)		
D3 – Psychological				
1 - High negative impact OHRQoL	76 (58.9)	109 (61.2)	0.680	1.05 (0.81 – 1.38)
0 - Low negative impact OHRQoL	53 (41.1)	69 (38.8)		
D4 - Self-image/social interaction				
1 - High negative impact OHRQoL	113 (87.6)	161 (90.4)	0.403	1.17 (0.80-1.71)
0 - Low negative impact OHRQoL	16 (12.4)	17 (9.6)		

OHRQoL: Oral Health-Related Quality of Life (OHRQoL); D: Domain. Poisson univariate regression model, with significance level of 0.05. Bold indicate statistical significance.

Table 3. Association between *TNF-* α gene (rs1799964, rs1799724, rs1800629) and OHRQoL in the group of children with caries experience and high severity caries-active

Variable		OHRQoL									
		Child subscale		D1-Symptoms		D2-Function		D3-Psychological		D4-Self-image/ social interaction	
		Median (Q1-Q3)	p-value	Median (Q1-Q3)	p-value	Median (Q1-Q3)	p-value	Median (Q1-Q3)	p-value	Median (Q1-Q3)	p-value
TNF-α rs1799964											
Caries experience											
Dominant model	CC + CT (56)	4 (0–7)	0.595	0 (0–1)	0.310	2 (0–4)	0.447	0 (0–2)	0.948	0 (0–0)	0.701
	TT (57)	3 (0–6.5)		0 (0–0)		2 (0–3)		0 (0–2)		0 (0–0)	
Recessive model	CC (14)	4 (2.25–8)	0.272	0 (0–2)	0.045	2 (0.75–4.25)	0.440	1 (0–2)	0.562	0 (0–0)	0.671
	CT + TT (99)	3 (0–6)		0 (0–0)		2 (0–4)		0 (0–2)		0 (0–0)	
High severity caries-active											
Dominant model	CC + CT (14)	5 (2.75–8)	0.977	0 (0–2)	0.084	2.5 (0.75–5.25)	0.841	0 (0–2.25)	0.752	0 (0–0)	0.931
	TT (10)	4 (2–9.5)		0 (0–0)		2.5 (2–4.5)		0 (0–2)		0 (0–0)	
Recessive model	CC (6)	7 (3.75–9.5)	0.177	1.5 (0–2.25)	0.033	3.5 (1.75–6.5)	0.454	1 (0–2.5)	0.494	0 (0–0.5)	0.721
	CT + TT (18)	4 (2–7.5)		0 (0–0)		2.5 (1.5–4)		0 (0–2)		0 (0–0)	
TNF-α rs1799724*											
Caries experience											
Dominant model	TT + TC (20)	2.5 (1–6)	0.731	0 (0–0.75)	0.945	1.5 (0–2)	0.226	0 (0–3)	0.876		0.776
	CC (96)	4 (1–7)		0 (0–0)		2 (0–4)		0 (0–2)			
High severity caries-active											
Dominant model	TT + TC (2)	4 (3–**)	0.400	2 (2–2)	0.086	1.5 (0–**)	0.286	1.5 (1–**)	0.533		0.857
	CC (19)	6 (4–9)		0 (0–1)		4 (2–6)		0 (0–2)			
TNF-α rs1800629 *											
Caries experience											
Dominant model	AA + AG (17)	4 (1–9)	0.643	0 (0–2)	0.215	2 (0–4)	0.862	2 (0–2)	0.319		0.819
	GG (93)	4 (0–7)		0 (0–0)		2 (0–4)		0 (0–2)			
High severity Caries-active											
Dominant model	AA + AG (1)	11 (11-11)	0.300	0 (0-0)	0.700	7 (7-7)	0.200	2 (2-2)	0.600		0.900
	GG (19)	6 (3-8)		0 (0-1)		3 (2-5)		0 (0-2)			

Q1 = percentile 25, Q3= percentile 75; Mann-Whitney test, with significance level of 0.05; bold indicates statistical significance. *Mann-Whitney Test cannot be performed on recessive models' due empty groups; **empty number.

genetic predisposition contributes to the perception of HRQoL.[7] In individuals requiring orthognathic surgery, depression, temporomandibular disorders, and genetic polymorphisms in IL6 were shown to contribute to a negative impact on OHRQoL.[21] Polymorphisms associated with the ANKK1 gene were related to positive impacts on women aged ≥ 30 years who underwent orthognathic surgery.[20] In para athletes with caries experience, the A allele in the IL1A gene (rs17561), in a dominant model, had a significantly higher risk of poor psychological discomfort than in those with the other allele.[32] To the best of our knowledge, this is the first report investigating *TNF*-α as a biomarker for OHRQoL. It is important to highlight here that *TNF*-α is a pleiotropic regulatory cytokine produced by several cell types that can exert a variety of roles and effects on cellular and biological processes, including immunity and inflammation.[33] Cytokine genetic pathways have been highlighted as candidate genes in a study investigating the molecular aspects of QoL.[7] In fact, our study found an association between rs1799964 and OHRQoL in children with dental caries. We hypothesize that this association may be due to the pleiotropic biological effects of TNF-α, which is known to influence cellular function in almost all cell types, and its inflammatory role, which is associated with pain perception.[7]

Based on the results presented in this study, we can confirm our hypothesis that *TNF*-α is a possible biomarker for OHRQoL in children with caries experience and with high-severity active caries. Major biological pathways are involved in each domain of the quality of life. In HRQoL, the inflammatory pathway has the strongest evidence as a mechanism to control underlying fatigue.[4] *TNF*-α has been associated with this type of domain in HRQoL.[7,11] In the present study, considering the child subscale, the symptom domain was negatively affected. This domain includes pain-related limitations. Psychological factors can strongly influence people's perception of pain, particularly chronic pain and sometimes pain-related disability. Almost all types of pain have a physical basis. However, psychological factors such as anxiety and depression can make people less able to control their symptoms and, therefore, are less able to perform their normal activities. Therefore, it is suggested that these children are more susceptible to worse responses to social interaction, and because of this, the psychosocial aspect should be considered. The conceptual framework (Figure 2) illustrates the complex interaction of the factors involved in poor OHRQoL in children with dental caries.

The GeneQoL Consortium has presented abundant evidence that genes influence personality traits substantially.[7] Much remains to be understood regarding how and why this is the case. Therefore, studies that place the behavioral genetics of personality within the context of epidemiology, evolutionary psychology, and neighboring psychological domains such as interests and attitudes would help lead to new insights.[34] Most of the research in the social sciences is seriously compromised if it does not incorporate genetic variation in its exploratory models.

Originally, dentistry had a predominantly restorative orientation. Gradually, with the basic ideas and principles of preventive dentistry being incorporated, health has increasingly a holistic and

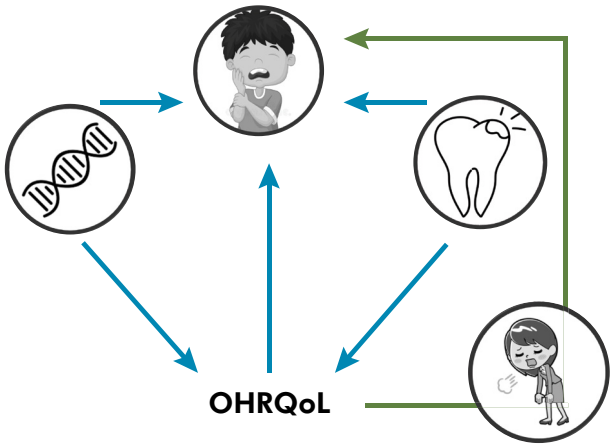

Figure 2. Conceptual framework: Oral Health-Related Quality of Life in patients with Dental caries and the influence of polymorphisms in *TNF*-α gene. Polymorphisms in gene *TNF*-α are related to impact on OHRQoL in chidren with dental caries mainly related to symptom domain(pain). The psychological factors can influence strongly on pain perception. The gray arrows correspond to the hypothesis discussed based from other studies of *TNF*-α influence on OHRQoL. The studies indicated that the inflammatory pathway has the strongest evidence as the mechanism to control underlying fatigue.

expanded view of the patient; therefore, further studies that include genetics and OHRQoL are needed. In the near future, genetics and the OHRQoL may become standard practices in dental clinics and educational institutions.

The research participants were adequately treated by the Department of Pediatric Dentistry of a public institution. After treatment, participants entered a rigorous six-monthly periodic follow-up program and continued to be accompanied by undergraduate students at the institution. There is no operational cost for this monitoring within the institution, as it is a public institution or university. However, to extrapolate the research results to the general population in the future, it would be interesting to investigate children in private institutions such as dental clinics and private offices. It would also be valuable for future research to investigate regular periodic monitoring to assess whether the possible biomarker could influence the child's perception of OHRQoL in the long term after treatment.

A limitation of this study is that it is one of the first studies to search for genetic markers involved in OHRQoL. This study aimed to assess children with dental caries in a single population. However, it is necessary to include different populations to identify novel candidate genes for OHRQoL. The OHRQoL instruments have been validated in several languages, allowing replication of our results in different countries.

Genetic polymorphisms in *TNF*-α are associated with OHRQoL in the symptom domain (pain), suggesting that *TNF*-α could be used as a potential biomarker for OHRQoL. Understanding the genetic aspects associated with OHRQoL will allow the early identification of patients with OHRQoL disparities and provide personalized healthcare.

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