Personalized Precision Medicine (PPM): A Tailored Treatment Approach for the Betterment of Prognosis in Oral Carcinoma: A Systematic Review

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Abstract

Background: The Personalized Precision Medicine (PPM) MODEL encompasses a custom-built treatment modality incorporating immunotherapy in the form of Monoclonal antibodies, checkpoint inhibitors, cytokines, hematopoietic stem cell transplants predominantly, and Chimeric Antigen Receptor T-cell (CART) therapies. Biomarkers, companion diagnostics, and Organoids are major tools in PPM to develop patient-specific databases, delivering patient-specific medicines for a targeted approach. **Objective:** To assess how efficacious personalized precision medicine can be in the betterment of prognosis comparison to traditional treatment strategies when treating oral cancer. **Methods:** Comprehensive search with PubMed, Cochrane library, Web of Science, Embase, and EBSCO health. ProQuest and Google scholar was looked up to find any further gray literature that might have been missed. After thoroughly assessing the studies for eligibility criteria, data were extracted by two reviewers, and a detailed quality check of the selected records was assessed via the Cochrane risk of bias-2 tool. **Results:** Nine articles were included in the systematic review after thorough screening and the removal of duplicates, by analyzing the title and abstract, concentrating on the connection between genomics and precision medicine and their effects on oral cancer. **Conclusions:** The advanced personalized precision medicine (PPM) ecosystem amalgamates established clinical data with genetic molecular profiling to fabricate tailored treatment plans for individual patients, thereby significantly improving prognosis.

Keywords: Biomarkers, genomics, oral cancer, precision medicine, prognosis

Introduction

India contributes to one-third of the total oral cancer burden and holds the second-highest position globally[1] The 5 years survival rate for oral squamous cell carcinoma (OSCC) is quite low, averaging at 50%–60%, with an 80% range for stage I tumors to about 40% for advanced stage IV malignancies, regardless of diagnostic and technological developments. Diagnostic delay and comparatively high rates of tumor recurrence observed in these patients can help explain this discrepancy. Approximately only 33% of patients are diagnosed at an early stage.[2,3] Traditional treatment options such as surgery, chemotherapy, and radiotherapy not only entail adverse effects but also have poor prognostic value. Immunotherapy has paved way for a personalized precision medicine (PPM) treatment model, which curates individualized treatment plans for patients. This overcomes barriers of traditional therapies, such as vast variations in treatment response and the harmful impact on non-cancerous tissues and organs. Customized therapeutic plans exclusive to particular tissues, genetic mutations, and personal patient features corresponding to a specific case describe the PPM strategy.[4]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/aomr

DOI: 10.4103/jiaomr.jiaomr_125_24

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How to cite this article: Pagare S, Shetty N, Bhor K, Chakraborty A, Waghmare M, Bhutani H. Personalized precision medicine (PPM): A tailored treatment approach for the betterment of prognosis in oral carcinoma: A systematic review. J Indian Acad Oral Med Radiol 2025;37:5-12.

Received: 17-04-2024 **Revised:** 16-11-2024
Accepted: 21-12-2024 **Published:** 29-03-2025

Aim

The purpose of this study was to conduct a systematic review focused on the evaluation of the "Effectiveness of Personalized Precision Medicine in the betterment of prognosis in the treatment of oral cancer in comparison with traditional treatment techniques".

Methodology

Registration and research protocol

The PROSPERO database has this systematic review registered under the ID: CRD42023451289, following the (PRISMA) Preferred Reporting Items for Systematic Reviews and Meta-Analysis principles.

Information sources

Pubmed, Cochrane library, Web of Science, Embase, and EBSCO health. ProQuest and Google scholar was looked up to find any further gray literature that might have been skipped. Time frame: January 2013 to March 2023.

Systematic search strategy (PICOS STARTEGY)

To integrate pertinent keywords and (MeSH) Medical Subject Heading Terms, Boolean operators (AND, OR) were utilized. The above-mentioned databases were searched using a strategy adopted by combining keywords and the PICOS selection criteria for qualitative synthesis.

Focused research question

How effective can the technique of personalized precision medicine be in improving the prognosis of oral carcinoma patients as compared to traditional treatment techniques?

PICOS selection criteria

Inclusion criteria

- Population: Only Oral (SCC) squamous cell carcinoma patients above 18 years.
- Intervention: Precision medicine and its prognostic implications in OSCC.
- Comparison: Patients may or may not be undergoing standard treatment regimens.
- Outcome: Impact of PPM on the prognosis in OSCC.
- Study Design: Randomized Controlled trials and CLINICAL trials,

Only Free full-text, open-access articles in English from 2013 to 2023.

Exclusion criteria

- *In Vitro* Studies (Animal studies)
- Case series/reports, Off-topic and review articles, Comments and Letters
- Paid, non-English articles beyond publication year 2013 and 2023
- Articles relating to the role of precision medicine in other head and neck disorders apart from OSCC.

Study selection

There were two phases to the article selection process. In the first review phase, two authors (AC and SP) independently assessed the references' titles and abstracts. Articles that didn't seem to fit the requirements for inclusion were disqualified. Complete chosen articles were then independently assessed by the same authors in phase 2. Discussions were used to settle any disputes. A third author was brought in to reach a verdict when two reviewers could not agree on anything. The complete content of the publication served as the foundation for every decision.

Assessment of risk of bias (ROB)

Cochrane Collaboration Tool 16 assessed the risk of bias for the chosen randomized controlled trials (RCTs), which covers allocation concealment, random sequence generation, participant blinding, etc., Using Minors' checklist, quality evaluation of non-randomized studies was conducted, and a minimum of 1 week of follow-up was deemed adequate for the included articles [Tables 1 and 2].

The respective graphs for the assessment of risk of bias were generated using Review Manager 5.4 [Figures 1 and 2]. (*attached separately*)

Study selection

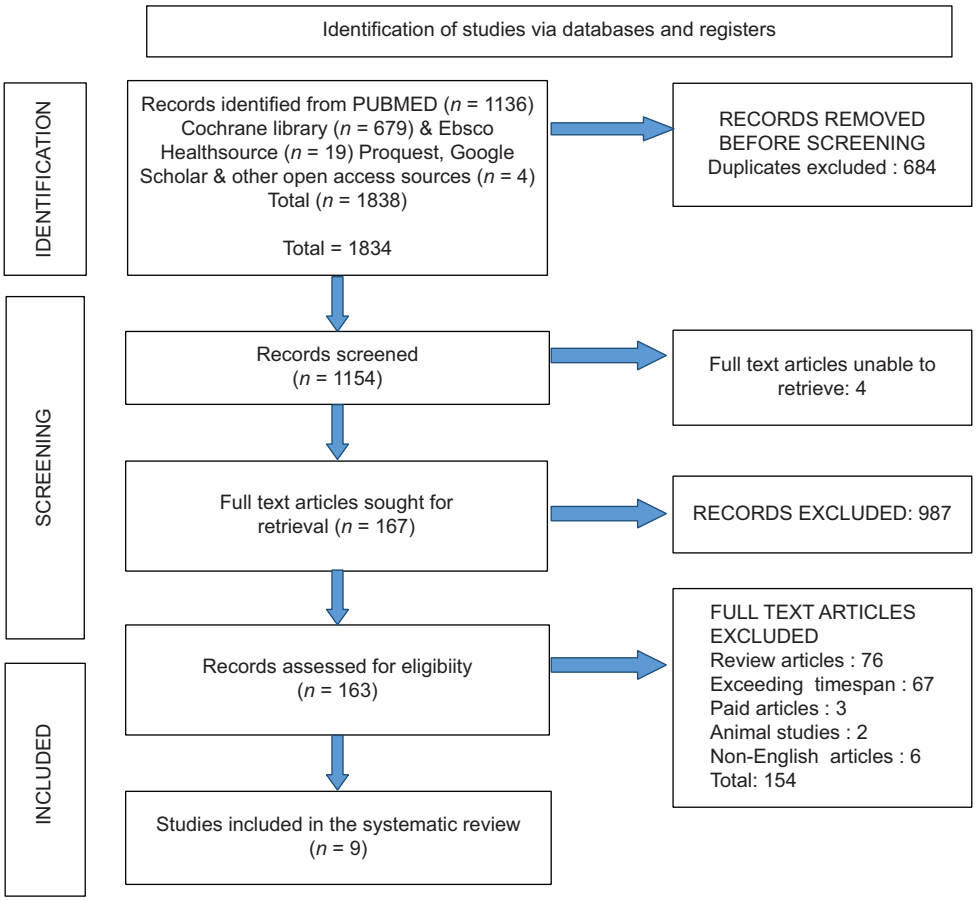
An outline of information flow through various review process steps is depicted in the Literature Search Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Study Characteristics

An overview of the detailed Data Extraction Sheet comprising traits of the featured articles is given in Flowchart 1.

Table 1: Risk of bias assessment for randomized controlled trial performed by Cochrane ROB tool

	Cochrane risk-of-bias tool for randomized trials							
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting	Others	Overall risk of bias
Dong Wang Zhu *et al*. 2013	Low	Low	Unclear	Low	Low	Low	Low	Low risk
C.Z.Yang *et al*. 2014 *et al*.	Low	Low	Low	Unclear	Low	Low	Low	Low risk
D.Zhu *et al*. 2014	Low	Low	Unclear	Low	Low	Low	Low	Low risk
Pierre Saintgny *et al*. 2017	Low	Low	Low	Unclear	Low	Low	Low	Low risk
Xianjun Shen *et al*. 2018	Unclear	Unclear	Low	Unclear	Low	Low	Low	High risk
Wu tong Ju *et al*. 2020	Low	Low	Low	Low	Low	Low	Low	Low risk



Flowchart 1: (PRISMA) Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 Flowchart for screening and selection criteria

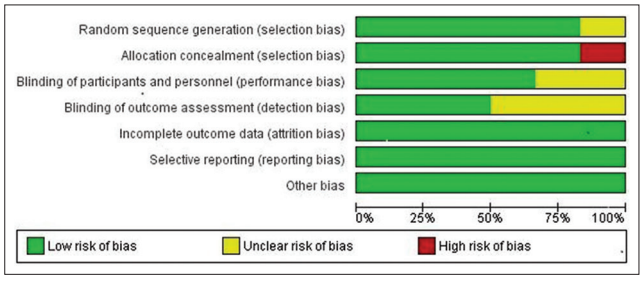


Figure 1: Risk of bias graph

Results

Study characteristics

Nine studies were included in this systematic review, comprising six RCTs and three clinical or experimental studies. Geographically, most of the studies were conducted in China (five studies), with others from Malaysia, Taiwan, the United States, and the United Kingdom. The studies focused on the evaluation of various biomarkers (Annexin A1, GDF-15, PLCG1, PD-L1, MET, HLA-G, and Stathmin) and prognostic outcomes in OSCC [Table 3a].

The included participants were primarily adults aged over 18 years. Gender distribution was not consistently reported across all studies, but in studies that did mention it, males generally comprised a higher proportion.

Objectives

The overarching objective across the studies was to assess the prognostic value of specific biomarkers and tumor-associated proteins in OSCC. Some studies additionally examined the role of combined clinicopathological and genomic variables in improve survival predictions and treatment outcomes.

Methods used

The studies employed diverse methodologies to evaluate the biomarkers and survival outcomes. Immunohistochemistry (IHC) analysis was the predominant method for assessing biomarker expression. Other methods included machine learning algorithms (Siow-Wee-Chang *et al.*), real-time PCR (Xianjun Shen *et al.*), and genome-wide expression profiling (Pierre Saintigny *et al.*). Survival outcomes were analyzed using statistical tools such as Kaplan-Meier analysis, Cox proportional hazards model, Chi-square tests, and Student's t-tests, with *P* values reported to indicate statistical significance.

Outcomes

Key biomarkers analyzed across the studies demonstrated significant correlations with survival parameters, including overall survival (OS), disease-free survival (DFS), distant metastasis-free survival (DMFS), and recurrence-free survival (LRFS). For example [Table 3b]:

Table 2: Risk of bias assessment for non-randomized control trial performed by MINORS checklist tool

	Methodological index for non-randomized studies (minors)												
	A clearly stated aim	Inclusion of consecutive patients	Prospective of collection of data	End points appropriate to the aim of study	Unbiased assessment of study endpoint	Follow up period appropriate to the aim of study	Loss to follow up <5%	Prospective calculation of study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analysis	Total
Siow-Wee-Chang 2013	2	2	2	2	0	2	2	0	1	1	0	1	15
Yueh-Min-Lin 2015	2	2	2	2	1	2	2	0	0	0	0	2	15
D.M. Zielecka-Debska 2017	2	2	2	2	0	2	2	0	0	0	0	2	14

Using MINORS, scores can be assessed as 0–4=very low quality; 5–8=low quality; 9–12=moderate quality; 13–16=high quality; and 19–24 very high quality

Figure 2: Risk of bias summary

- Annexin A1: Low expression was associated with improved DFS ($P = 0.036$) and LRFS ($P = 0.031$).
- GDF-15: Low expression predicted better OS ($P = 0.049$) and DMFS ($P = 0.031$).
- PLCG1: Low expression correlated with better OS ($P = 0.035$), DFS, LRFS, and DMFS.
- PD-L1: High expression was significantly associated with distant metastasis ($P = 0.0103$) and poorer prognosis in males ($P = 0.0077$) and smokers ($P = 0.0004$).
- MET: High expression led to decreased oral cancer-free survival ($P < 0.001$).
- MCM7: Significantly impacted 5-year OS ($P = 0.041$).
- HLA-G: Higher expression was linked to advanced TNM stages and lymph node metastasis ($P < 0.05$).
- Stathmin: Low expression predicted improved survival following TPF chemotherapy ($P = 0.028$).

Siow-Wee-Chang *et al*. uniquely applied machine learning methods to combine genomic and clinicopathologic markers, achieving a predictive accuracy of 93.81%, which highlights the potential of hybrid analytical techniques.

Bias and quality assessment

The quality of studies was assessed using the Cochrane Risk of Bias-2 tool for RCTs and the MINORS checklist for

Table 3a: Data extraction sheet of recorded studies.[5-13]

General characteristics of the included studies							
Author Year	**Country**	**Study design**	**Parameter of precision medicine assessed**	**Total no. Of oscc patients**	**Age of patients**	**Gender of patients**	**Loss to follow up or dropouts**
Dong Wang Zhu 2013	China	RCT	Annexin A1	256	NR	NR	24(patients lost due to unsatisfactory specimen)
Siow-Wee-Chang 2013	Kuala- Lumpur, Malaysia	Experimental study	Feature selection & Machine learning methods for clinicopathologic markers	31	NR	NR	3 were lost to follow up at the end of 3 years
C.Z.Yang 2014	China	RCT	GDF-15	256	NR	NR	26 patients lost to follow up over 3 years.
D.Zhu 2014	China	RCT	PLCG-1	256	.NR	NR	Three patients were lost to follow-up over 5 years
Yueh-Min-Lin 2015	Taiwan	CT	PDL-1	305	Age group <56: 162 patients Age group: > or=56: 143 patients	Female patients: Male patients: 236	NR
D.M. Zielecka-Debska 2017	London, UK	CT	MCM-7	129	NR	NR	NR
Pierre Saintgny 2017	Chicago , USA	RCT	MET	86	NR	NR	NR
Xianjun Shen 2018	China	RCT	HLA-G	52	NR	28 males and 24 females	NR
Wu tong Ju 2020	China	RCT	Stathmin	256	Age: 26-75 years; mean age: 55.4 years	NR	86 samples were excluded because of low quality or quantity of tissues.

non-randomized studies. Among the RCTs, five were rated as low risk of bias, while one study (Shen et al., 2018) was deemed high risk due to unclear blinding and allocation processes. For non-randomized studies, the MINORS scores ranged between 14 and 15, indicating moderate to high quality.

Heterogeneity

The included studies demonstrated heterogeneity in terms of study design, biomarkers evaluated, methods of assessment, and survival parameters analyzed. While no formal statistical assessment of heterogeneity (e.g. Chi-square test) was conducted due to the nature of the review, variability in sample size and biomarker endpoints contributed to observational heterogeneity.

Meta-analysis

A meta-analysis was not performed in any of the included studies due to differences in biomarkers, study endpoints, and methodological approaches.

Discussion

All the studies in the review corroborated with the fact that incorporating genomic variables in the treatment of oral cancer can significantly improve prognosis in OSCC patients. More tests and experiments need to be performed to further verify the results obtained from the studies included in this systematic review.

Incorporating precision medicine into dental practice represents a significant advancement for patients with oral cancer, steering the field toward a more targeted and less invasive approach. This shift emphasizes personalized treatment strategies that are tailored to the individual characteristics of each patient's condition, leading to more effective and less intrusive interventions.[14]

Every practitioner should guide their patients with suspected malignant/premalignant lesions to several advanced medical centers and laboratories that specialize in precision medicine and oncology. Utilization of genomic profiling to identify mutations or genetic predispositions linked to oral cancer should be done. This can guide treatment decisions, such as choosing specific therapies that target molecular pathways associated with the patient's cancer type.

Risk Stratification Using genetic information, along with environmental and lifestyle factors (like tobacco use, alcohol consumption, HPV status), to assess the patient's risk and develop personalized prevention strategies should be incorporated. If the patient's cancer exhibits specific genetic mutations, you can collaborate with oncologists to recommend targeted therapies, such

Table 3b: Data extraction sheet of recorded studies.[5-13]

Outcome of the included studies									
Author Year	**Experimental group**	**Control group**	**Outcome variables**	**Method of Assessment**	**Assessment sessions**	**Statistical analysis:**	***P***	**Results**	**Conclusion**
Dong Wang Zhu 2013	105	127	OS - DFS/LRFS/DMFS	IHC analysis .	3	- Chi-square test - Kaplan-Meier method - Log-rank test -HR from Cox proportional hazards model	Survival analysis: Better DFS (P=0.036, HR=0.620) for low Annexin A1 expression.	- Low Annexin A1 expression: Lower local recurrence rate. -	Annexin A1 may be a prognostic biomarker for OSCC.
Siow-Wee-Chang 2013	31	10	- Group 1: Clinicopathologic variables *- Group 2: Clinicopathologic and genomic variables **	- Five feature selection methods	1(upto 3 years)	NA	NA	The model with the best accuracy (93.81%) is the Relief-GA 3-input model from Group 2.	Prognostic results are more accurate when combining clinicopathologic and genomic markers.
C.Z.Yang 2014	104	126	OS DFS/LRFS/DMFS	IHC analysis .	3	-Chi-square test - Kaplan-Meier method - Log-rank test - HR from Cox proportional hazards model	Better OS (P=0.049, HR=0.597) and DMFS (P=0.031, HR=0.562)	- Low GDF15 expression: Better OS &DMFS	GDF15 expression could serve as a predictive biomarker for OSCC.
D.Zhu 2014	128	125	OS - DFS/LRFS/DMFS	IHC analysis	3	-Chi-square test - Kaplan-Meier method - Log-rank test - (HR) from Cox proportional hazards model.	Better OS (P=0.035) and better DFS (P=0.155), LRFS (P=0.086), and DMFS (P=0.095)	Low PLCG1 expression :.Better DFS, LRFS, and DMFS.	PLCG1 could be prognostic biomarker in locally advanced OSCC.
Yueh- Min-Lin 2015	305	NA	Clinicopathological parameters*	IHC Analysis	NR	- Chi-square test - Kaplan-Meier method - Log-rank test - HR from Cox proportional hazards model.	Distant metastasis (P=0.0103) In male: P=0.0077; in smoker: P=0.0004)	High PD-L1-expression was significantly associated with distant metastasis.	PD-L1 was found to be an independent prognostic marker in male patients and smokers, which was confirmed by multivariate analysis.
D.M. Zielecka-Debska	129	NA	LRFS, DFS, DSS & OS	IRS, the percentage of stained cells (MCM7%) and the INT.	NR	- Chi-square test	5 year-OS P=0.041	MCM7- INT had a statistically signiflcant impact on 5 year-OS	MCM7 INT and MCM7 IRS can be a good prognostic biomarker in OSCC.
Pierre Saintgny 2017	35	51	OCFS	Immunostaining & Genome-Wide Expression	1	Student's *t* test. The Kruskal-Wallis	OCFS (P<0.001)	OCFS was significantly decreased in patients with high MET	MET expression by IHC may represent new target

Contd...

Table 3b: Contd...

Outcome of the included studies									
Author Year	**Experimental group**	**Control group**	**Outcome variables**	**Method of Assessment**	**Assessment sessions**	**Statistical analysis:**	***P***	**Results**	**Conclusion**
				Profiles of Oral Leukoplakias collected prospectively.		test		expression levels	for chemoprevention.
Xianjun Shen 2018	52	20	Clinicopath-ological parameters*	IHC analysis, RTPCR	Not specified	Pearson Chi-square test	Higher HLA-G expression observed in advanced TNM stages ($P<0.05$).	HLA-G expression was positively associated with TNM stage and lymph node metastasis	HLA-G expression could be a potential biomarker for OSCC
Wu tong Ju 2020	92	78	Clinicopathological variables *	IHC Analysis	1	Student t tests. one-way analysis of variance	Stathmin expression ($P=0.004$). OS from TPF induction chemotherapy ($P=0.028$)	TNM Stage IVa: high stathmin expresion, Low stathmin expression: improved OS from TPF chemotherapy	Stathmin expression could be a potential as a biomarker for guiding TPF treatment.

NR=Not reported, OSCC=Oral squamous cell carcinoma, RCT=Randomized controlled trial, CT=Clinical trial. OS=Overall survival, DFS=Disease free survival, LRFS=Locoregional recurrence free survival, DMFS=Distant metastasis free survival, DSS=Disease specific survival, OCFS=Oral cancer free survival, IHC=Immunohistochemistry, INT=Intensity of the color reaction, HR=Hazard ratios, TPF=Docetaxel, Carboplatin and Fluorouracil, GDF-15=Growth differentiation factor, PLCG-1=Phospholipase C gamma1, PDL-1=Programmed Cell Death Ligand, MET=mesenchymal-epithelial transition factor, MCM-7=minichromosome maintenance complex component 7, HLA-G=Human Leucocyte Antigen-G, RTPCR=Real-time reverse transcription-polymerase chain, NA=Not Applicable. *Clinicopathologic variables: (15 variables) Including: tumor size, site, stage, differentiation subtype, depth of invasion, treatment type such as gender, histological grade, lymph nodal metastasis, and TNM stage were analyzed. **Genomic variables :(17 variables) Including: p53 and p63 tumor suppressor genes

as MET, PDL-1 inhibitors for certain mutations. Regular biomarker monitoring that indicates the cancer's response to treatment or the likelihood of recurrence should be encouraged. Patients should be educated on the benefits and limitations of precision medicine, enabling them to make informed decisions about their care.[15]

Guidance based on their lifestyle changes that complement their personalized treatment plan, such as dietary adjustments or smoking cessation, based on their genetic risk should be given.

Dental practitioners should adopt a multidisciplinary approach, working closely with oncologists, genetic counselors, and other specialists to integrate precision medicine into the patient's overall treatment plan. Dental professionals should also stay updated on the latest advancements in precision medicine through continuous education and collaboration with research institutions.

By integrating precision medicine into dental practice, we can provide more effective, personalized care for patients with oral cancer, improving outcomes and quality of life.[16]

Strengths of the review

Biomarker-Based Diagnosis and Prediction Models

- Accuracy in Diagnosis: Biomarkers help in accurately identifying the nature of tissues, thereby assisting in both the diagnosis and post-treatment monitoring of oral cancer.
- Prognostic Value: Precision medicine, guided by biomarker testing, is crucial for assessing the prognosis of oral cancer rather than oral diseases in general. This approach helps in understanding the likely course of the disease and personalizing treatment plans accordingly.

Importance of Early Diagnosis

- Survival Rates: Early diagnosis is crucial for improving survival rates in oral cancer patients. When identified at an early stage, the survival rate is approximately 90%, often achievable with a single surgical therapy.
- Functional Outcomes: Early intervention can also help preserve function, as tissue defects caused by surgery can be fully compensated, leading to better quality of life post-treatment.

Limitations of the review

1. Cohort-Specific Findings: The association between Met expression and the time to oral cancer (OC) development was observed in a single patient cohort with a small sample size from a randomized clinical trial that lacked a placebo arm. Further validation in independent cohorts, particularly those not receiving experimental therapies, is necessary.
2. Survival Metrics: The study evaluating the prognostic role of PDL-1 focused on overall survival without assessing relapse-free or disease-free survival, limiting the understanding of the disease's progression and recurrence.
3. Cost and Standardization Challenges: Despite the promise of personalized precision medicine, the lack of standardization and high upfront costs remain significant drawbacks. However, the approach holds potential for developing better-targeted therapies by accumulating individualized genomic data in patient-specific databases.

Conclusion

This review underscores the transformative potential of precision medicine and biomarkers in oral cancer care, highlighting how these advancements can lead to more accurate diagnoses, better prognostic insights, and improved therapeutic outcomes, particularly when the disease is detected early.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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