PATHFINDER OF RESEARCH

Review Research

Improving Treatments for Oral Diseases, Head and Neck Cancers, as well as Developing New Technologies

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Abstract: Head and neck cancers, encompassing malignancies of the oral cavity, pharynx, and larynx, represent a considerable worldwide health concern, with over 890,000 new cases and 450,000 deaths each year. Notwithstanding progress in conventional therapies like surgery, radiation, and chemotherapy, the outcomes remain inadequate, particularly for recurrences or metastases. This review synthesizes current medicinal and technological breakthroughs aimed at improving clinical outcomes and patient quality of life in oral and head and neck cancers. Molecular profiling has discovered changes in genes like TP53 mutations, EGFR overexpression, and issues with the PI3K/AKT/mTOR system, which assist in developing personalized cancer treatments. Immunotherapy, particularly treatments that focus on PD-1/PD-L1, offers long-lasting results for certain groups of patients identified by specific markers. Nanotechnology-based drug delivery systems improve targeted therapy by increasing the amount of medicine at tumor sites and reducing side effects in nearby tissues. Artificial intelligence (AI) has transformed disease diagnostics, facilitating earlier identification and customized treatment strategies. Liquid biopsies facilitate the early detection of illnesses and their ongoing monitoring. Regenerative medicine employs stem cell treatment, 3D bioprinting, and CRISPR gene editing to restore bodily functions and enhance tumor targeting. Digital health instruments such as wearable biosensors, tele-oncology, and patient reporting systems enhance therapy precision and monitoring.

Keywords: Oral cancer, Immunotherapy, Nanomedicine, Biomarkers, Regeneration, Diagnostics

Article History:
Received: 11 January 2025
Accepted: 20 March 2025
Online: 22 March 2025

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Citations: Akhter, S., Ansari, M. A. S., Tiva, M. G. & Bhuyian, M. S. (2025). Improving Treatments for Oral Diseases, Head and Neck Cancers, as well as Developing New Technologies. *Pathfinder of Research*, *3*(1), 1-25

1. Introduction

Head and neck cancers (HNCs), which include malignancies of the oral cavity, pharynx, and larynx, remain a considerable public health problem globally. According to GLOBOCAN 2020, head and neck cancers (HNCs) account for around 890,000 new cases and 450,000 deaths annually, or over 5% of all cancer cases worldwide **(Sung et al., 2021)**. The prognosis for several patients is bleak, with 5-year survival rates at 50%, particularly in late stages marked by recurrence and metastasis **(Johnson et al., 2020)**. This persistent dilemma underscores the critical need for both preventative strategies and novel treatment interventions. The etiology of head and neck cancers is complex and multifactorial. Tobacco and alcohol consumption are the primary risk factors, accounting for almost 70% of cases. Concurrent consumption elevates cancer risk by 30 to 40 times relative to abstainers **(Hashibe et al., 2009).** In South and Southeast Asia, betel quid (areca nut) substantially increases the prevalence of oral cancer **(Gormley et al., 2022).** Human papillomavirus (HPV), especially type 16, is now the main cause of oropharyngeal cancer in many wealthy countries, with HPV-positive cases often seen in younger people and having better outcomes **(Johnson et al., 2020).** The Epstein-Barr virus (EBV) is strongly linked to nasopharyngeal cancer, especially in endemic regions **(Gormley et al., 2022).** Other factors, such as poor oral hygiene, periodontal disease, and nutritional deficiencies, have also been linked, but to a lesser degree **(Meurman, 2010)**. Socioeconomic disparities significantly influence the prevalence and effects of disease, with marginalized populations exhibiting heightened risk and reduced access to timely care **(Conway et al., 2018).**

Despite advancements in clinical care, traditional treatment modalities surgery, radiation, and chemotherapy remain prevalent persist in demonstrating considerable constraints. These operations are often invasive and lead to functional impairments affecting speech, swallowing, and appearance, resulting in lasting reductions in quality of life **(Lo Nigro et al., 2017).** Additionally, treatment results often plateau when cancer recurs or metastasizes. Standard methods struggle to address tumor heterogeneity and immune evasion, limiting their effectiveness. These problems have led to an increased focus on targeted, less detrimental, and more personalized therapeutic approaches. Recently, immunotherapy has emerged as a substantial advancement in the treatment of head and neck cancer. Immune checkpoint drugs that focus on PD-1 and PD-L1 have helped patients with recurring or spreading head and neck cancer who didn't respond to regular treatments live longer **(Kaidar-Person et al., 2018)**. These medications represent a substantial shift toward precision oncology, where treatments are informed by tumor-specific immunological and genomic attributes. However, their effectiveness is often limited to specific groups of people identified by biomarkers, showing the need for better prediction tools and combination treatment strategies **(Marur & Forastiere, 2016; Ortiz-Cuaran et al., 2021**). Concurrently, artificial intelligence (AI) transforms diagnostic and therapeutic approaches in head and neck cancer (HNC). AI-supported imaging, analysis of medical images, and

study of tissue samples have made it easier to diagnose and find early signs of cancerous changes. Artificial intelligence models are employed in treatment planning to predict tumor behavior, optimize radiation doses, and improve the accuracy of surgical margins **(Pham et al., 2024).** Although still in its early stages, AI can personalize treatment and enhance complex decision-making processes. Nanomedicine has considerable transformative potential. Nanoparticle-based drug delivery systems can boost the amount of medicine at tumor locations while reducing harm to the rest of the body. This targeted approach is particularly advantageous in HNC, as surrounding healthy tissues have increased sensitivity **(Li et al., 2024).** Researchers are looking into using nanocarriers to deliver chemotherapy drugs, radiosensitizers, and immunomodulators, which could help overcome resistance in tumors that keep coming back or don't respond to treatment. Besides medical procedures, head and neck malignancies exert considerable mental and economic consequences. Patients often experience deformity, impaired speech, and social isolation, resulting in heightened anxiety, sadness, and reduced quality of life **(Nayak et al., 2022).** The economic impact of HNC involves significant healthcare costs due to the requirement for multidisciplinary therapies, rehabilitation, and extended follow-up care. In the United States, yearly direct medical expenditures exceed $3.5 billion, while indirect costs from reduced productivity intensify the total burden **(Wissinger et al., 2014).**

Despite the significant preventability of head and neck cancers, global preventive measures remain underutilized. Initiatives for tobacco and alcohol cessation, including HPV vaccination and community-based screening, can significantly reduce disease incidence. However, inequities in healthcare access and resource allocation continually hinder implementation, particularly in low- and middle-income countries **(Gormley et al., 2022).** This research aims to provide a comprehensive summary of current advancements in treatments and technology for oral and head and neck cancers. We examine progress in molecular profiling, immunotherapy, nanomedicine, diagnostics, artificial intelligence integration, and regenerative techniques. We focus on translational gaps, clinical application, and patient-centered outcomes, providing a sophisticated viewpoint to guide research, practice, and policy.

2. Methodology

A narrative synthesis method was utilized to collect and examine peer-reviewed literature regarding therapeutic and technical advancements in oral and head and neck malignancies. We searched databases like PubMed, Scopus, Web of Science, and Google Scholar for articles published between 2017 and 2025 using keywords such as 'oral cancer,' 'head and neck squamous cell carcinoma,' 'immunotherapy,' 'precision oncology,' 'nanotechnology,' 'CRISPR,' '3D bioprinting,' and 'AI in oncology.' The inclusion criteria were English-language, peer-reviewed studies, reviews, and clinical

trials concentrating on developments related to oral and head and neck cancers (HNCs). Editorials, non-peer-reviewed materials, and unrelated research were omitted. Out of an initial pool of 130 sources, 85 were chosen based on their relevancy and quality. Articles were organized using Zotero, and data were thematically classified to illustrate current trends and clinical significance.

3. Results and Discussion

3.1 Molecular and Genetic Landscape of Oral and Head and Neck Cancers

3.1.1 TP53 Mutations and p53 Gain-of-Function Mechanisms

TP53 is the most often altered gene in head and neck squamous cell carcinoma (HNSCC), with inactivating mutations present in around 60-80% of cases **(Li et al., 2023).** HPV-negative tumours notably demonstrate a high frequency of TP53 mutations, predominantly of the missense variety, while HPV-positive tumours typically preserve wild-type TP53; in these cases, the p53 protein is functionally inactivated by viral oncoproteins **(Johnson et al., 2020).** In addition to the loss of tumour-suppressor function, numerous mutant p53 proteins exhibit gain-of-function (GOF) characteristics that actively facilitate oncogenesis **(Li et al., 2023).** GOF p53 mutations can induce genomic instability, augment invasion and metastasis, and impart resistance to therapy in HNSCC cells **(Li et al., 2023)**. Common missense mutations in the DNA-binding domain (e.g., R248, R273) not only impair p53's cell-cycle arrest and apoptosis functions but also confer new oncogenic activities to the protein, including the transactivation of proliferation pathways and the alteration of the tumour microenvironment **(Johnson et al., 2020; Li et al., 2023).** The mutation status of TP53 is clinically associated with aggressive disease and adverse prognosis in individuals with HNSCC **(Farah, 2021).** These observations have prompted initiatives to restore or target mutant p53; for example, experimental pharmaceuticals that reactivate wild type p53 signalling or promote the degradation of mutant p53 are currently under investigation **(Islam et al., 2025).** Although these therapies are not yet conventional, the widespread involvement of p53 dysfunction in HNSCC positions it as a focal point in the disease's molecular framework.

3.1.2 Changes in the Pathway of PI3K/AKT/mTOR and EGFR

A key feature of oral and head and neck squamous cell carcinoma (HNSCC) is the improper control of growth factor signaling, particularly with the EGFR and PI3K/AKT/mTOR pathways. Many HNSCC tumors have higher protein levels, and around 10-15% have localized gene amplification; EGFR is often overexpressed (Johnson et al., 2020). This activation is linked to aggressive tumor characteristics and drives cancer cell growth **(Farah, 2021; Grau et al., 2022).** Though it has modest effectiveness, the authorized therapy is the anti-EGFR antibody cetuximab. HNSCC often has changes in the PI3K-AKT-mTOR pathway, which is affected by EGFR, and PIK3CA mutations are found in 10–20% of cases, particularly in HPV-positive throat cancers. These mutations, along with PTEN loss and AKT

amplification, cause uncontrolled mTOR signaling, which supports cell growth and survival. Though issues like toxicity and resistance still exist, clinical studies are assessing many inhibitors aimed at this route **(Johnson et al., 2020; Farah, 2021).** At the same time, activating both the EGFR and PI3K pathways could lead to resistance to single treatments, which is why researchers are looking into combination therapies **(Farah, 2021).** HNSCC has various subgroups based on the causes of the disease and genetic differences, showing a lot of clinical and molecular variety **(Johnson et al., 2020).** Compared to HPV-negative cancers, which are often genetically unstable, HPV-positive tumors often have fewer mutations and a better prognosis **(Farah, 2021).** Gene expression research categorizes HNSCC into at least four inherent subtypes: Basal, Mesenchymal, Classical, and Atypical **(Sunny et al., 2020).** Every subtype has certain traits, including the Basal subtype's EGFR pathway activation and the Mesenchymal subtype's EMT hallmark **(Farah, 2021).** Immune profiling also sets cancers as "immune-active" or "immune-exhausted" **(Burtness et al., 2019).** The intratumor heterogeneity of HNSCC, which comprises many subclonal populations, influences different treatment reactions and recurrence risk **(Johnson et al., 2020).** Current studies seek to use this diversity for precision oncology, customizing therapies depending on the genetic profile of the cancer **(Cao et al., 2021).**

3.2 Viral Oncogenesis: Epstein-Barr Virus and Human Papillomavirus

Viral oncogenesis is quite important in some head and neck malignancies, particularly due to high-risk human papillomavirus (HPV) in oropharyngeal carcinoma and Epstein-Barr virus (EBV) in nasopharyngeal carcinoma. Particularly that caused by HPV16, HPV-related head and neck squamous cell carcinoma (HNSCC) has a unique pathophysiology in which the E6 and E7 oncoproteins interfere with important tumour suppressors, therefore causing uncontrolled cell cycle progression and malignant transformation **(Johnson et al., 2020; Li et al., 2023; Nakagawa et al., 2021).** HPV-positive cancers usually do not have mutations in TP53, show high levels of p16^INK4A^, which indicates that the pRb pathway is not working properly, and often respond better to treatment and have a better outlook than HPV-negative tumours. Their genomic profile sets them apart from HPV-negative tumours by fewer mutations and particular activating mutations in PIK3CA as well as changes in TRAF3 and CYLD **(Farah, 2021; Nakagawa et al., 2021).**

By contrast, EBV-associated nasopharyngeal carcinoma (NPC) is related to latent EBV infection in cancerous cells; almost all undifferentiated NPCs in East Asia have clonal EBV genomes **(Lee et al., 2021)**. EBV promotes cancer development by producing hidden viral proteins and non-coding RNAs that change how cells work, particularly through the latent membrane protein 1 (LMP1), which affects the NF-κB and MAPK signalling pathways. In NPC, EBV infection is linked to a "methylator" phenotype defined by broad promoter hypermethylation and silence of tumour suppressor genes **(Nakagawa et al., 2021).** With latent proteins drawing epigenetic changes to encourage cancer, EBV-

positive NPC tumours have more abnormal DNA methylation than most HPV-negative HNSCC (Su et al., 2023). Clinically relevant is the discovery of viral drivers in both tumours; HPV status is a typical prognostic factor in oropharyngeal carcinoma, and EBV status is vital for NPC diagnosis. Both viruses generate gene products that can be targeted for treatment, such as therapeutic vaccines and adoptive T-cell treatments for EBV antigens in NPC, and immunotherapeutic targets for HPV oncoproteins E6/E7 in HPV-related HNSCC **(Johnson et al., 2020; Su et al., 2023).**

3.3 Dysregulation of Epigenetics and Non-Coding RNAs

Beyond genetic defects, dysregulation of epigenetics and non-coding RNAs is a key factor in the complexity of head and neck squamous cell carcinoma (HNSCC). Often, unusual DNA methylation patterns mute tumor suppressor genes; in tobacco-related oral cancers, promoter hypermethylation usually inactivates the CDKN2A gene **(Nakagawa et al., 2021)**. HPV-negative and HPV-positive HNSCC reveal different DNA methylation patterns; HPV-driven cancers have more hypermethylated CpG islands because viral oncoproteins influence host DNA methyltransferases **(Nakagawa et al., 2021).** By suppressing genes connected to cell cycle control, apoptosis, and DNA repair, these epigenetic alterations can encourage cancer development.

Though their patterns are complicated and under-researched, histone changes and chromatin remodeling also play a role in HNSCC. HNSCC is notably dysregulated by non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), which influence gene expression. Some miRNAs are oncogenes or tumor suppressors; miR-21 is a well-known oncomiR overexpressed in HNSCC that drives tumor growth by downregulating PTEN and other PI3K/AKT pathway targets **(Sunny et al., 2021).** High miR-21 levels are linked to more invasion, treatment resistance, and worse prognosis, which prompts studies on miR-21 inhibitors as a possible therapy. On the other hand, several miRNAs that suppress cancerous processes, such as members of the miR-99 family and miR-125b, are typically downregulated in oral cancers **(Cao et al., 2021).**

Tumor-suppressive miRNAs' depletion causes overexpression of their targets and uncontrolled cell growth. lncRNAs have become important HNSCC regulators affecting cancer biology by several means, including recruiting epigenetic enzymes, sequestering miRNAs, or functioning as transcription factor decoys **(Cao et al., 2021)**. Overexpressed in several head and neck malignancies, the lncRNA HOTAIR silences genes inhibiting spread by enlisting Polycomb complexes. HNSCC often has lower levels or increased methylation of MEG3, another lncRNA that helps prevent tumors **(Cao et al., 2021**). Similarly, aggressive HNSCC exhibits elevated MALAT1, a signal that promotes the epithelial-mesenchymal transition (EMT) and its dissemination. Often, changed gene expression resulting from

these non-coding RNA changes favor neoplastic pathways.

3.4 Uses of Precision Oncology and Improved Biomarkers

Precision oncology methods are being developed thanks to a better understanding of the molecular structure of head and neck squamous cell carcinoma (HNSCC), where specific biomarkers guide targeted therapies or personalized treatment plans. Among the important new uses and key biomarkers are:

PD-L1 Expression A key factor that helps predict how well immunotherapy will work in head and neck squamous cell carcinoma (HNSCC) is whether programmed death-ligand 1 (PD-L1) is found on tumor or immune cells. In tumors that have a lot of PD-L1, immune checkpoint inhibitors-anti-PD-1/PD-L1 antibodies-have been effective for treating recurrent or metastatic HNSCC. Patients with tumors that have high PD-L1 levels (Combined Positive Score ≥20) experienced a notable improvement in survival when treated with the first-line therapy pembrolizumab in the KEYNOTE-048 study **(Burtness et al., 2019).** People with high PD-L1 levels are more likely to respond to pembrolizumab or nivolumab, while those with low or no PD-L1 may require different treatments, so PD-L1 testing is now commonly used to determine the best therapy for patients. Though not a flawless substitute, PD-L1 is still the best marker for spotting HNSCC responders **(Burtness et al., 2019**). Beyond PD-L1, research is still being done to find alternative immunotherapy biomarkers, including immune gene signatures and tumor mutational burden, to enhance patient selection **(Johnson et al., 2020; Ribas & Wolchok,2021).**

Though uncommon (4-8% of HNSCC), HRAS mutations have drawn interest as a targetable molecular grouping. Though rather aggressive, HRAS-mutant HNSCC is especially responsive to farnesyltransferase inhibitors, which prevent RAS protein synthesis. In HRAS-mutant HNSCC, the farnesyltransferase inhibitor tipifarnib was very effective, showing about a 55% success rate in a Phase II study **(Ho et al., 2021).** Pending more approvals, this prompted the FDA to give tipifarnib in HRAS-mutant head and neck cancer Breakthrough treatment status, showing how an oncogenic driver mutation may be exploited for targeted treatment **(Ho et al., 2021; Ifty et al., 2024).**

Other Actionable Changes and PIK3CA Among the most prevalent oncogenic occurrences in HNSCC are PIK3CA mutations. Researchers are investigating PIK3CA-mutant HNSCC with various PI3K-selective medications (e.g., alpelisib) and PI3K/mTOR inhibitors, either individually or in combination **(Johnson et al., 2020).** Early research shows little effectiveness and difficulties in defeating resistance mechanisms. Researchers are also investigating personalized treatments using other genetic changes, such as NOTCH1 (inactivating mutations), CCND1 (cyclin D1 amplifications), MET, and FGFR1. Though "actionable" mutations are detected in just a tiny proportion of patients, restricting the broad use of targeted medicines, the aim is to match more patients with subtype-specific treatments as

genomic profiling progresses **(Farah, 2021).**

Viral DNA and Circulating Tumor DNA (ctDNA) methods of liquid biopsy are becoming useful in controlling head and neck malignancies. In oropharyngeal carcinoma linked to HPV, circulating tumor Higher levels of HPV DNA in the blood can indicate a return of oropharyngeal cancer months before it is clinically detected, making it a useful tool for checking the disease status in HPV-related cases **(Chera et al., 2020).** A 2020 clinical trial indicated that tracking plasma HPV DNA had a high positive predictive value for identifying recurrent or residual illness, thereby integrating it into follow-up procedures at some centers **(Chera et al., 2020)**. With higher pre-treatment levels suggesting worse outcomes, plasma EBV DNA is a marker linked to tumor load and prognosis in EBV-driven nasopharyngeal cancer **(Lee et al., 2021).** Clinical practice in endemic locations increasingly incorporates EBV DNA detection for screening, staging, and early relapse recognition **(Lee et al., 2021).** A major study found that checking plasma EBV DNA improved the early detection of nasopharyngeal cancer and increased survival rates.

3.5 Advances in Therapeutics

3.5.1 Conventional to Contemporary Shifts

Treatment for head and neck cancer has evolved from traditional methods like surgery, radiation, and chemotherapy to more advanced technologies that aim to reduce side effects while achieving good outcomes. Surgical innovations include microvascular reconstructive techniques and organ-preserving approaches, including transoral robotic surgery. Improving tumor targeting and normal tissue protection, radiation treatment has moved from two-dimensional planning to more exact modalities, including intensity-modulated radiation therapy and proton therapy, therefore lowering treatment side effects and enhancing local control rates **(Ifty et al., 2023b; Contrera et al., 2025).** Particularly with platinum-based schedules like high-dose cisplatin, chemotherapy is quite important for locally advanced cancer treatment as well as palliative care for recurring or metastatic illness. A significant improvement in targeted treatment is the addition of cetuximab, an antibody that targets EGFR, to platinum-5FU chemotherapy in the EXTREME regimen, which has notably increased the average survival time for patients with recurrent or metastatic HNSCC from about 7.4 to 10.1 months **(Vermorken et al., 2008).** Though many patients still have locoregional recurrence or metastasis, the general survival rate for advanced head and neck squamous cell carcinoma (HNSCC) has not improved much in recent years despite these developments. Surgical restrictions include, among others, inoperability.

3.5.2 Immunotherapy & Checkpoint Inhibitors

Immunotherapy has transformed head and neck cancer treatment by using immune checkpoint

inhibitors that "re-activate" T cells to target tumor cells, focusing on the PD-1/PD-L1 and CTLA-4 pathways. PD-1 is a receptor on active T cells that connects with the higher levels of PD-L1 found on cancer cells, which reduces the activation of T cells (**Mahin et al., 2021; Fahad et al., 2022**). By helping T cells work better, anti-PD-1 antibodies like nivolumab and pembrolizumab allow the immune system to attack cancer (Mei et al., 2020). CTLA-4 stops T cells from being activated; anti-CTLA-4 antibodies like ipilimumab help activate T cells in lymphoid organs. Instead of directly killing cancer cells, these treatments enhance the immune reaction. Especially for recurring or metastatic situations, clinical effectiveness has been remarkable. Nivolumab improved the average survival time from 5.1 to 7.7 months compared to standard treatment, making pembrolizumab and nivolumab the first anti-PD-1 monoclonal antibodies to show better overall survival in head and neck squamous cell carcinoma (HNSCC). In patients with recurrent or metastatic HNSCC that have PD-L1, pembrolizumab also significantly improved survival rates **(Burtness et al., 2019).** However, there are challenges because only 15–20% of HNSCC patients respond to PD-1 blocking treatment on its own, and many tumors show resistance early on. Regulatory T cells and myeloid-derived suppressor cells are two examples of elements that might compromise immune function. Only recurrent or metastatic cancer currently has authorization for immunotherapy, and studies for first treatment have yielded mixed results **(Lee et al., 2023).** Combination treatments have shown some effectiveness; using both PD-1 and CTLA-4 inhibitors together does not extend life compared to standard treatment **(Haddad et al., 2023; Ifty et al., 2023a).** Current studies aim at maximizing patient selection and investigating new immune agonists and checkpoints to defeat resistance. Treating advanced head and neck cancer still depends much on immune checkpoint blockade; current research is to determine its best integration **(Mei et al., 2020; Sharon et al., 2023).**

3.5.3 Targeted Therapies and Combination Regimens

Targeted medicines and combination regimens are being created to target the molecular weaknesses of head and neck malignancies, especially head and neck squamous cell carcinoma (HNSCC). The first targeted treatment for HNSCC, cetuximab, works against the epidermal growth factor receptor (EGFR), which is overexpressed in around 90% of HNSCC patients, hence encouraging cancer cell proliferation and survival. Approved in 2006, cetuximab has demonstrated better survival rates when used with platinum-based chemotherapy **(Vermorken et al., 2008)** and radiation treatment (Bonner et al., 2010). Many patients, meanwhile, show cetuximab resistance; efforts to increase its effectiveness with alternative EGFR inhibitors have mostly failed; the FDA has not now authorized any EGFR tyrosine kinase inhibitors for head and neck cancer. Though bigger studies are required to validate their efficacy, VEGF pathway antagonists and multi-kinase inhibitors are being investigated in relation to other targets, including angiogenesis **(Mehanna et al., 2021)**. The PI3K-AKT-mTOR pathway is also

being studied; buparlisib shows slight survival benefits when used with paclitaxel (Bello et al., 2020). These inhibitors have not yet been approved by the FDA, however, because of restricted effectiveness and adverse effects.

Genomics-based precision medicine seeks to customize therapies to particular cancer mutations. Although HNSCC contains several genetic changes, HRAS mutations stand out since they appear in 4-8% of patients. Tipifarnib has been classified as a breakthrough treatment as it has shown potential in treating HRAS-mutant HNSCC **(Ho et al., 2021).** Though uncommon, NTRK gene fusions can be addressed with TRK inhibitors such as entrectinib and larotrectinib, which have demonstrated great response rates **(Drilon et al., 2018).** Especially in some nasopharyngeal or sinonasal malignancies, pembrolizumab may help tumors with significant tumor mutational load or microsatellite instability. Many patients lack certain driver mutations; hence, precision treatment for head and neck cancer is still in its infancy.

There is increasing interest in combination regimens given the modest efficacy of single-agent treatments. Combining immunotherapy and targeted therapy might improve therapeutic effectiveness. Early studies indicate that combining PD-1 antagonists with EGFR inhibitors produces favorable response rates (KEYNOTE-137). With early findings indicating safety and efficacy, ongoing research is looking at combinations including nivolumab and cetuximab **(Chowdhury et al., 2021; Tian et al., 2025).** KEYNOTE-048, a conventional treatment for recurrent or metastatic cancer, demonstrates the use of chemotherapy in conjunction with immunotherapy. Trials such as PembroRad and JAVELIN Head & Neck investigate the possibility of combining radiation treatment with immunotherapy to boost immune responses. In HNSCC, dual checkpoint inhibition has not demonstrated better effectiveness **(Haddad et al., 2023**). Targeted drugs could possibly be combined with immunotherapy or other methods to overcome resistance, like using lenvatinib, which has shown response rates of 40-50% when paired with pembrolizumab.

Table 3: FDA-approved Drugs and Clinical Trials for Oral and HNC (2020–2024)

Therapy (Approval)	**Mechanism/Target**	**Indication (Trial/Year)**	**Key Outcomes**
Cisplatin (approved 1978) *	DNA crosslinking agent (chemotherapy)	Locally advanced HNSCC (definitive or adjuvant CRT)	Conventional radiosensitizer; enhances locoregional control and survival when used in conjunction with radiation **(Pignon et al., 2009)** meta-analysis. Constraints: significant toxicity (ototoxicity and nephrotoxicity).
Cetuximab	EGFR monoclonal	Locally advanced HNSCC	Radiation therapy: enhanced five-year

(approved 2006)	antibody	(with RT) (Bonner et al., 2010); Recurrent/metastatic HNSCC (EXTREME regimen, 2008)	overall survival rate of 45% compared to 36%**(Sharon et al., 2023).** EXTREME: enhanced median overall survival of 10.1 months vs to 7.4 months with chemotherapy alone **(Lee et al., 2024)**. Initial targeted therapy in HNSCC; advantages for a subset, with acneiform rash serving as a predictor of response.
Pembrolizumab (approved 2016; 2019 expansion)	Anti-PD-1 immune checkpoint inhibitor	Recurrent/metastatic HNSCC – second-line post-platinum (KEYNOTE-040, 2017); First-line recurrent/metastatic HNSCC, PD-L1-positive (KEYNOTE-048, 2019)	Second-line: improved 1-yr OS ~37% vs 26% (vs methotrexate) (Cohen et al., 2019). First-line: in CPS ≥1, improved OS (13.6 vs 10.4 mo); in CPS ≥20, 14.9 vs 10.7 mo. FDA-approved as monotherapy for CPS≥1 and with chemo for all comers.
Nivolumab (approved 2016)	Anti-PD-1 immune checkpoint inhibitor	Recurrent/metastatic HNSCC – platinum-refractory (CheckMate 141, 2016)	Improved median OS 7.7 vs 5.1 months vs docetaxel/methotrexate: 1-year OS ~36% vs 16%. Established new standards after platinum failure. Notable for doubling the 2-year survival rate (17% to 36%).
Durvalumab (approved 2020**)	Anti-PD-L1 immune checkpoint inhibitor	Recurrent/metastatic HNSCC – platinum-refractory (HAWK trial, 2020) *investigational in HNSCC*	HAWK: ~16% response in PD-L1-high HNSCC. Combination with CTLA-4 inhibitor tremelimumab in EAGLE trial showed no OS benefit over standard therapy (Ferris et al., 2020). Not FDA-approved for HNSCC (approved in other cancers).
Tipifarnib (Breakthrough designation 2021)	Farnesyltransferase inhibitor (targets HRAS)	HRAS-mutant recurrent/metastatic HNSCC (AIM-HN trial, 2021) *ongoing*	Phase II **(Ho et al., 2021**): 55% disease control rate; median PFS ~5.9 mo in post-platinum HRAS-mutant patients. Not yet FDA-approved (trial ongoing) but granted Breakthrough Therapy status due to encouraging efficacy in this subset.
Pembrolizumab + Platinum + 5-FU (approved 2019)	PD-1 inhibitor + cytotoxic chemotherapy	First-line therapy for recurrent/metastatic HNSCC (KEYNOTE-048, 2019)	Combination arm improved ORR (36% vs 20%) and 2-yr survival (à 28%) vs EXTREME regimen **(Lee et al., 2024)**. Became a new standard for PD-L1-unselected patients. Higher toxicity (e.g. myelosuppression) but no new safety

			signals.
Nivolumab + Ipilimumab (investigational)	PD-1 and CTLA-4 checkpoint blockade	First-line recurrent/metastatic HNSCC (CheckMate 651, final analysis 2023)	Did not significantly improve OS vs EXTREME in all patients (13.9 vs 13.5 mo) **(Haddad et al., 2023)**. In PD-L1 CPS ≥20 subset, showed a trend to benefit but not statistically significant. Highlighted tolerable safety but underscored need for better biomarkers.
Afatinib (no FDA approval in HNSCC)	EGFR tyrosine kinase inhibitor (ErbB family blocker)	Recurrent/metastatic HNSCC (LYNC trial, 2021)	Compared afatinib vs methotrexate: modest PFS improvement but no OS benefit **(Machiels et al., 2021)**. Significant toxicities (rash, diarrhea) led to lack of approval in HNSCC. Indicates limits of single-agent EGFR TKIs in this cancer.
Xevinapant (Phase III trials ongoing)	Inhibitor of apoptosis proteins (IAP) antagonist	Locally advanced, unresectable HNSCC (added to chemoradiation; Debio 1143 Phase II, 2020)	Phase II **(Le Tourneau et al., 2020)**: 2-yr locoregional control 54% vs 33% with CRT alone; median OS not reached vs 36.1 mo, HR 0.37. Garnered excitement as the first radiosensitizer to improve outcomes in decades. Phase III (TrilynX) initiated 2020; update 2023: trial halted early (no definitive results yet).
PDS0101 (HPV16 vaccine) + Pembrolizumab (investigational combo)	HPV16-specific therapeutic vaccine + PD-1 inhibitor	Recurrent/metastatic HPV-positive HNSCC (NCT04260126, interim 2022)	Phase II interim: ORR ~41% in checkpoint-nave, HPV16+ patients; median PFS ~10.4 mo, 1-yr OS 87% **(Strauss et al., 2023).** Suggests immunotherapy efficacy can be boosted by tumor-specific vaccines. Further evaluation in ongoing trial.

3.6 Advancing Therapeutics and Technologies for Oral Diseases and Head and Neck Cancers

3.6.1 Nanotechnology and Novel Drug Delivery Systems

Nanotechnology has developed different small carriers, like liposomes, dendrimers, polymeric nanoparticles, micelles, metallic nanoparticles, and magnetic nano systems, that use the special environment around tumors to improve drug delivery for head and neck cancers **(Chowdhury et al., 2020; Liang et al., 2021).** These carriers reduce systemic toxicity and raise drug concentrations at the tumor site, thereby improving localized drug delivery. Dendrimer-based carriers have many surfaces

to hold drugs, while liposomal formulations make water-resistant chemotherapy drugs work better **(Zhang & Dong, 2023).** Polymeric micelles support drug stability and help release them in the acidic environment of the tumor **(Liang et al., 2021).** Stimulus-responsive nanoparticles are a new way to deliver medications that release them when they sense certain signals from tumors, like low pH levels or things like infrared light **(Liang et al., 2021).** For example, gold nanocages release medications when they heat up, while pH-sensitive liposomes let go of their contents in acidic environments**.** For instance, gold nanocages can let go of medications when they get hot, while pH-sensitive liposomes release their contents in acidic conditions**.** For example, gold nanocages can release medications when heated, whereas pH-sensitive liposomes expel their payload in acidic environments**.** By adding specific molecules to the surface of nanoparticles that target tumors, we can better focus on cancer cells and reduce side effects on healthy cells **(Chowdhury et al., 2020; Sun et al., 2023).**

Although various nanoparticle-based treatments are under clinical trials for head and neck tumors, none have been authorized by the FDA for this use**.** Especially in advanced situations, nab-paclitaxel has performed well when combined with chemotherapy and cetuximab, reaching a 76.3% response rate **(Weiss et al., 2023).** Investigational treatments such as BIND-014 have also shown acceptable toxicity and effectiveness**.** In studies, inorganic nanoparticles like NBTXR3 are being tested as radio-sensitizers and have been proven to be safe and somewhat effective so far **(Sunny et al., 2025b).** New advancements in nanomedicine include better forms of paclitaxel that work more effectively against tumors and magnetic nano-liposomes that help deliver treatments directly to the affected area**.** Methods like delivering siRNA along with chemotherapy aim to alter the tumor environment and make treatments more effective**.** Strategies such as co-delivery of siRNA with chemotherapy also seek to change the tumor microenvironment and improve treatment effectiveness **(Liang et al., 2021)**. To defeat tumor defenses, nano-immunotherapy techniques are also under investigation **(Zhang & Dong, 2023).** In the end, current clinical trials are trying to see how well these new therapies work for patients with oral and head and neck cancers, making drug delivery with nanotechnology a promising way to enhance how effectively cancer treatments are delivered and targeted at the disease.

3.7 Technology in Diagnosis and Monitoring

Through interdisciplinary methods, improvements in diagnostic technology are improving the early diagnosis and monitoring of head and neck malignancies. Clinical imaging and pathology are using artificial intelligence (AI) and machine learning (ML) to find early-stage malignancies, often with more accuracy than human observers. For example, an artificial neural network identified high-grade dysplasia and oral cancer from benign lesions with almost 90% accuracy **(Chowdhury et al., 2022; Pham & Teh, 2024)**. AI-driven solutions like the Mobile Mouth Screening Anywhere (MeMoSA) app let you record and analyze oral lesion photos, showing 85-90% sensitivity in identifying high-risk

lesions **(Pham & Teh, 2024).** AI-powered cytology can also assess cell characteristics on its own, improving non-invasive screening.

Early detection and prognostication are also being transformed by "omics" technologies like genomics and proteomics. From minimally invasive samples like mouth rinses, high-throughput sequencing can reveal genetic changes and viral markers, thereby detecting oncogenic HPV types or TP53 mutations **(Islam et al., 2018)**. Research suggests that tests looking at multiple genes and proteins could help find head and neck squamous cell carcinoma before symptoms appear, and blood tests are creating indicators for spotting cancer early. Researchers have linked increased plasma DNA of tumor-specific mutations to early oral cancer detection **(Kumar et al., 2024).** Notable for their non-invasive cancer detection potential are liquid and salivary biopsies. Recent studies indicate excellent sensitivity and specificity for early cancer detection; saliva can produce many tumor biomarkers (Kumar et al., 2024). Plasma-based liquid biopsies can effectively track how the disease is progressing because they can find circulating DNA, which detects recurrences earlier than traditional imaging methods. People around the world are using these technologies in various ways, particularly in areas with limited specialized access **(Pham & Teh, 2024).** Improved early diagnosis and monitoring are being made possible by the combination of artificial intelligence, molecular biomarkers, and liquid biopsies; hence, possibly increasing survival rates by means of prompt therapies **(Pramesh et al., 2022).**

3.8 Regenerative and Precision Medicine

Progress in regenerative medicine and precision genomic therapy is opening new pathways for the treatment of oral and maxillofacial disorders and targeting cancer at its genetic origins. Patients with head and neck cancer may endure considerable tissue deficits or functional impairments following surgery or radiation therapy. Stem cell treatment has potential for regenerating tissues like jawbone and salivary glands, especially when using mesenchymal stem cells (MSCs) derived from sources such as bone marrow and adipose tissue. Preliminary studies indicate that injecting MSCs can help restore salivary gland function after radiation treatment, and early clinical trials show that cancer survivors have improved saliva production **(Upadhyay & Tran, 2023).** Additionally, researchers are looking into using bone grafts made with stem cells for repairing the jaw, using stem cells from patients in 3D-printed structures to effectively rebuild parts of the jawbone.

Precision medicine is advancing with CRISPR gene editing, which focuses on cancer-causing genes in tumor cells and boosts immunotherapy. CRISPR/Cas9 technology has been used to remove HPV oncogenes in oral cancer models and to improve T-cell changes for better tumor fighting **(Zhang et al., 2023).** Clinical studies using CRISPR-modified T cells are currently underway, showing promise in making T cells last longer and working better against tumors. As of 2025, no CRISPR-based therapy for head and neck cancer has obtained FDA clearance; nonetheless, swift improvements indicate that gene-

edited therapeutics may soon be accessible **(Rohaan et al., 2022; Sun et al., 2023).**

Additionally, 3D bioprinting and bio fabrication technologies are transforming maxillofacial reconstruction by producing living tissue constructs customized to individual anatomical specifications. Recent progress has made it possible to create bone pieces and soft tissue with blood vessels, which could replace parts lost to cancer **(Michelutti et al., 2025).** While fully functional 3D printing of organs is still being worked on, there have been significant successes like FDA-approved 3D-printed titanium implants for jaw repair and the first bio printed human trachea implant. Nonetheless, obstacles persist in the development of tissues, including blood arteries and neurons, and regulatory agencies exercise caution over the safety and usefulness of these technologies. The combination of regenerative techniques and precision medicine, shown by using a patient's induced pluripotent stem cells for bioprinting or fixing cancer-related mutations in cells taken from the patient, represents the future of personalized healthcare. As successful early research moves into clinical trials, stem cell treatment, gene editing, and bioprinting are expected to shift from being experimental to practical treatment options, aiming to not only eliminate cancers but also repair damaged tissues and functions.

3.9 Digital Health, mHealth, and Patient-Centric Innovations

Digital health solutions and mobile health (mHealth) technologies are improving the management of head and neck cancer by prioritizing patient welfare outside of clinical environments. Wearable biosensors, including smartwatches and fitness bands, provide the continuous observation of patients' physiological conditions and behaviors throughout therapy. A small study indicated that smartwatches could track heart rate and activity levels, revealing that less physical activity and a higher resting heart rate were linked to fatigue and dehydration caused by radiation, which requires quick action from doctors **(Holländer-Mieritz et al., 2023).** Although wearables have mostly been utilized to evaluate feasibility and patient compliance, they also possess the ability to predict outcomes such as unplanned hospitalizations **(Brandts et al., 2024).** Remote patient monitoring (RPM) solutions are using FDA-approved wearables to relay vital sign patterns to healthcare professionals, enabling timely treatments for problems **(Holländer-Mieritz et al., 2023).**

Tele-oncology technologies have proliferated markedly, particularly because of the COVID-19 epidemic, enabling patients to obtain follow-up care and symptom management from home through secure video conferencing. Studies demonstrate that telemedicine follow-ups are equally beneficial as in-person consultations for detecting recurrences and treating side effects while alleviating travel difficulties **(Darr et al., 2021)**. Telehealth initiatives have demonstrated cost-effectiveness, as research indicates decreased total expenditures and a reduction in emergency visits attributable to enhanced patient participation **(Xie et al., 2022)**. Moreover, telemedicine promotes multidisciplinary dialogue

beyond geographical limits, improving access to specialized treatment **(Patil et al., 2022).** Customization is essential to address patient demands, as not all individuals are at ease with virtual technology, resulting in hybrid care models that integrate telemedicine with in-clinic assessments.

Patient-reported outcomes (PROs) are essential for patient-centered innovation, utilizing standardized questionnaires to evaluate symptoms and quality of life. Adding PRO monitoring to regular treatment has shown better results in cancer care, as a study found that advanced cancer patients who used an online system to report their symptoms lived longer **(Basch et al., 2017).** Electronic Patient-Reported Outcomes (ePRO) systems allow patients with head and neck cancer, who have complex symptoms, to regularly report major symptoms, thus enabling prompt treatments **(Sazzad et al., 2024).** The APCOT study exhibited significant adherence to ePRO reporting and enhanced patient satisfaction with therapy, underscoring the advantages of computerized symptom monitoring **(Nicolay et al., 2023).**

Innovative mHealth applications for head and neck cancer offer tools for treatment monitoring, symptom documentation, and interactions with healthcare professionals. These applications can improve patient involvement and alleviate anxiety by serving as a "virtual companion" during therapy **(Carter et al., 2021).** Worldwide, digital health technologies are mitigating disparities by disseminating expertise to remote regions via programs such as Project ECHO and employing simple mobile phone follow-ups in low-income nations to monitor postoperative patients. We anticipate that the growing affordability of digital gadgets will expand their utilization in cancer treatment. In conclusion, patient-centered innovations in digital health are transforming supportive care and follow-up in head and neck cancer. Technologies like wearables and electronic patient-reported outcome (ePRO) systems change treatment from reacting to problems after they happen to actively monitoring patient health all the time, even outside the hospital. Telehealth and mHealth enable patients to engage actively in their healthcare, thereby improving medical results and increasing patient happiness and quality of life. As digital health advances, it will be imperative to tackle obstacles like data privacy and fair access to effectively incorporate new technologies into holistic head and neck cancer therapy.

3.10 Policy, Access, and Equity

Despite progress in treatments and technology, considerable discrepancies in access to these advances remain across high-income countries (HICs) and low- and middle-income countries (LMICs), as well as among various groups within the same nation. The exorbitant expense of innovative treatments, such as immune checkpoint inhibitors, is a significant obstacle, especially in economically disadvantaged areas. A study in India found that only 2.8% of patients who could benefit from checkpoint inhibitors for head and neck and lung cancer received them, mainly due to high costs and difficulties in getting treatment, with noticeable differences based on social and gender factors **(Patil et al., 2022).** In wealthy countries, people are closely examining whether these treatments are worth the

money, as shown by a review of nivolumab in the United States, which found that the costs are much higher than what most people are willing to pay. Pembrolizumab has superior cost-effectiveness in specific subgroups; nonetheless, there is agreement that costs must be reduced or specialized funding methods implemented **(Chan et al., 2021).**

Access to sophisticated technology is inconsistent, since several low- and middle-income countries (LMICs) lack vital radiation equipment, resulting in suboptimal results for patients with head and neck cancer. The five-year survival rate for head and neck cancer is around 50% in developed areas, although it may fall below 20% in certain locations of South Asia and Africa **(Sullivan et al., 2022).** Diagnostic techniques are frequently constrained in low-resource environments, leading to late-stage identifications and obsolete therapies. Rectifying these gaps needs synchronized governmental initiatives and international cooperation. Strategies encompass tiered pricing, generic production, and infrastructural investments. Countries such as India and Brazil are manufacturing biosimilar monoclonal antibodies at reduced costs to enhance affordability. Highlighting prevention and early detection, including HPV vaccination and screening, is essential **(WHO, 2020).** The WHO targets a "30% reduction in cancer mortality by 2030," advocating for enhanced access to prompt detection and treatment **(WHO, 2020).** Certain LMICs have effectively incorporated oral cancer screening into primary care, improving early detection.

Public-private partnerships and international investment are crucial in enhancing accessibility. Organizations such as the UICC and ASCO give mentorship to cancer institutions in economically disadvantaged regions, while charitable initiatives supply discounted pharmaceuticals to specific patients. Nonetheless, these initiatives just fulfill a small portion of the demand. The WHO's proposed "Cancer Equity Fund" might pay for costly treatments in resource-constrained environments. Policy strategies to enhance equality encompass the expansion of insurance coverage and the allocation of funds for novel cures. Specialized authorization pathways for costly therapies facilitate resource optimization. Manufacturers are under pressure to adjust their pricing based on patient outcomes through the implementation of value-based care frameworks. Access to clinical trials is essential, as economically disadvantaged persons frequently lack possibilities for participation. Improving trial infrastructure and accelerating the approval of biosimilars and generics can save expenses **(Patil et al., 2022; JCO Global Forum, 2023).** Ultimately, fortifying health systems is vital. Numerous oral cancer patients in low-income countries exhibit advanced, inoperable tumors resulting from insufficient healthcare access. Investments in general care, oral health services, and oncology education can effectively address these disparities. Rwanda's telepathology networks illustrate technology-driven fairness by enabling expedited cancer diagnostics. In summary, attaining parity in head and neck cancer therapy necessitates comprehensive initiatives. High-income countries must negotiate fair

pricing and evaluate cost-effectiveness, but low- and middle-income countries require assistance to improve capacity and access to vital therapies. Global policy frameworks, such as the WHO Global Initiative for Cancer Care, underscore the significance of inclusion in healthcare innovations **(Pramesh et al., 2022; Mithun et al., 2024).** Rectifying the equity gap is both an ethical obligation and a pragmatic requirement for global health, since enhancing outcomes in head and neck cancer can substantially diminish avoidable morbidity and mortality.

3.11 Future Perspectives and Research Priorities

The area of oral and head and neck oncology is on the brink of a substantial revolution owing to breakthroughs in nanotechnology, artificial intelligence, gene editing, and digital health. The forthcoming decade is anticipated to witness an increase in customized, technology-driven, and multidisciplinary healthcare. A major trend is the rise of "theragnostic" nanoparticles that can diagnose, treat, and monitor responses all at the same time. These smart nanoparticles can act as both MRI contrast agents and cancer drugs, responding to signals from tumors and providing feedback through imaging **(Sun et al., 2023).** Prospective nanomedicines may integrate biosensors for instantaneous monitoring of medication release and tumor conditions.

Artificial intelligence is expected to assume a more significant role in clinical practice, perhaps utilizing federated learning to integrate multimodal data for complete decision support **(Pham & Teh, 2024).** Artificial intelligence systems may aid in treatment suggestions and diagnostics, while explainable AI algorithms can bolster physician trust by elucidating predictive aspects. Artificial intelligence may assist in forecasting treatment results and undesirable effects, requiring interdisciplinary collaboration to guarantee that AI solutions address clinical requirements and undergo appropriate validation. Precision medicine will enhance therapy selection with complete genome sequencing, facilitating customized therapies based on tumor vulnerabilities. New pharmacological targets are anticipated to arise from genome research, and immunotherapy will be customized utilizing diverse indicators. Investigations are now being conducted on therapeutic cancer vaccines and adoptive cell treatments for head and neck malignancies **(Sunny et al., 2025a).**

Regenerative medicine is poised to progress beyond mere structural regeneration, with prospective uses of bio-scaffolds fed with patient cells for tissue regeneration following surgical procedures. In situ 3D bioprinting has the potential to produce patient-specific implants, tackling vascularization issues and maintaining biomechanical integrity. Regulatory frameworks must evolve to accommodate distinctive bio printed tissues. Digital health and patient interaction will advance, with remote monitoring and mHealth applications improving patient rehabilitation. Telemedicine, along with AI-driven technologies, will optimize routine follow-ups, prioritizing patient-centric design. Collaborative efforts that are interdisciplinary and multinational are crucial for tackling intricate cancer issues.

Research goals are enhancing outcomes in resource-limited environments and emphasizing value-based innovations **(Pramesh et al., 2022).** Adaptive trial designs and the collection of real-world evidence will enhance the discovery of effective therapies. Bridging translational gaps is essential for ensuring that laboratory findings are accessible to patients, especially given the rarity and variety of head and neck malignancies. The future of head and neck oncology will be defined by the amalgamation of scientific disciplines, therapeutic approaches, and cutting-edge technology with public health concepts. Current investigations in nanotechnology, artificial intelligence, CRISPR, and digital health seek to improve survival rates, functional preservation, and quality of life for those with oral disorders and head and neck malignancies.

4. Conclusion

The way we treat oral, and head and neck cancers has changed a lot, moving from standard surgery, radiation, and chemotherapy to more targeted approaches like immunotherapy and precision medicine. Immunotherapy, especially immune checkpoint inhibitors, has greatly improved treatment results for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), while targeted therapies show potential for specific genetic groups. The integration of nanotechnology, CRISPR, regenerative medicine, and AI-driven diagnostics is poised to markedly improve therapeutic efficacy and early detection. However, challenges persist, such as the limited utilization of combination therapy, the poor implementation of breakthrough technologies, and disparities in access to modern treatments. To turn these scientific findings into real benefits for patients, future efforts need to focus on teamwork in innovation, equal access to healthcare, personalized treatments based on biomarkers, and effectively using new technologies. These initiatives will be essential for achieving sustainable disease management, enhanced quality of life, and improved survival rates for patients worldwide.

Funding

This work had no outside funding.

Author Contribution

The authors were involved in the creation of the study design, data analysis, and execution stages. Every writer gave their consent after seeing the final work.

Acknowledgments

We would like to thank the authors of the reviewed articles

A statement of conflicting interests

The authors declare that none of the work reported in this study could have been impacted by any known competing financial interests or personal relationships.

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