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REVIEW ARTICLE

Oral adverse drug reactions in precision oncology: A phenotype-first framework for causality, triage, and treatment continuity

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Abstract

Introduction: Precision oncology has broadened the spectrum of oral adverse drug reactions (ADRs), while combination regimens and common oral diseases complicate their recognition and attribution.

Objectives: To propose a phenotype-first framework for assessing suspected oral ADRs, guiding triage and management, and supporting anticancer treatment continuity.

Methods: A manual literature search was conducted in PubMed/MEDLINE and Google Scholar using combinations of keywords such as "oral adverse drug reactions," "oral toxicity," "precision oncology," "immune checkpoint inhibitors," "targeted therapy," "oral mucositis," "xerostomia," "medication-related osteonecrosis of the jaw," "oral lichenoid reactions," and "supportive care." Relevant studies and clinical guidelines were synthesized narratively to develop a phenotype-first framework.

Results: The framework considers lesion morphology and functional impact alongside treatment chronology, host factors, local dental conditions, targeted investigations, and response to intervention. It addresses immune-inflammatory and lichenoid disease, aphthous-like or mucositis-like ulceration, salivary and taste dysfunction, secondary infection, and impaired wound or bone healing. Combining phenotype with diagnostic certainty and clinical severity informs proportionate action, from local supportive care and reassessment to urgent specialist evaluation and oncology coordination. Structured documentation and patient-reported outcomes can support longitudinal assessment and pharmacovigilance.

Conclusion: Phenotype-first reasoning may help clinicians distinguish suspected treatment toxicity from competing or coexisting oral conditions and manage reversible symptoms without unnecessarily disrupting cancer therapy. Severe, persistent, atypical, or diagnostically uncertain findings require timely interdisciplinary assessment. Prospective evaluation is needed to establish the framework's reproducibility and clinical utility.

Keywords: Oral adverse drug reactions; Precision oncology; Pharmacovigilance; Oral medicine; Immune-related adverse events; Medication-related osteonecrosis of the jaw

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1. Introduction

Oral adverse drug reactions (ADRs) are frequently treated as a subsidiary component of systemic toxicity, yet they can directly influence pain, nutrition, speech, oral hygiene, sleep, and willingness to continue treatment. In precision oncology, this problem has become more complex because immune modulation, pathway inhibition, vascular interference, and suppression of bone remodeling produce oral presentations that are less predictable than conventional cytotoxic mucositis. The resulting lesions may be clinically mild but persistent, or they may become dose-limiting, infectious, or destructive when they are recognized late.[1,2]

A drug-centered catalog is useful for anticipating toxicity, but it is insufficient for everyday diagnosis. The same patient may receive immunotherapy, a targeted agent, corticosteroids, antiemetics, antimicrobials, and a bone-modifying drug, while also carrying periodontal disease, prosthetic trauma, xerogenic medications, or previous head and neck radiotherapy. Under these conditions, oral erythema, ulceration, dryness, or pain cannot be attributed reliably from morphology alone. Different therapies converge on similar phenotypes, and common oral diseases can mimic treatment toxicity.[3-5]

This uncertainty matters because both errors have consequences. Over-attribution may lead to unnecessary interruption of an effective anticancer agent or inappropriate immunosuppression. Under-attribution may leave a clinically relevant immune-mediated lesion, severe salivary dysfunction, or early jaw necrosis untreated until function is compromised. The oral clinician therefore occupies a dual role: treating local disease while helping the oncology team judge whether the event is related to therapy and whether continuation is safe.[6-8]

Standard adverse-event terminology captures severity but often lacks the morphological and diagnostic detail required in oral medicine. Conversely, a detailed oral diagnosis may fail to communicate functional burden in a form useful to oncology. Bridging these perspectives requires a common structure that combines phenotype, impact on daily function, diagnostic certainty, and treatment response, while also incorporating patient-reported symptoms that may be underestimated during a brief clinical examination.[9,10]

This review therefore adopts a different perspective from conventional therapy-by-therapy summaries. Its central question is how a clinician should move from a new oral finding to an evidence-based treatment decision. The proposed framework is phenotype-first, causality-aware, and explicitly designed to preserve cancer-treatment continuity. It emphasizes what should be documented, which competing diagnoses should be excluded, when local management is sufficient, and when urgent oral medicine or oncology escalation is required.

2. Methodology

2.1. Narrative review methods and framework development

The literature was identified through a manual, topic-guided search of PubMed/MEDLINE and Google Scholar, using combinations of "oral adverse drug reactions," "oral toxicity," "precision oncology," "immune checkpoint inhibitors," "targeted therapy," "antibody-drug conjugates," "oral mucositis," "oral lichenoid reactions," "xerostomia," "medication-related osteonecrosis of the jaw," and "supportive care." Clinical practice statements, consensus recommendations, pharmacovigilance and observational investigations, clinical studies, and relevant narrative or systematic reviews were examined. The purpose was a clinically focused narrative synthesis, not an exhaustive retrieval; no prespecified screening counts, risk-of-bias grading, or meta-analysis are claimed.

Existing drug-specific recommendations, including the Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO) oral-toxicity statements, mucositis guidance, immunotherapy guidance, and medication-related osteonecrosis of the jaw (MRONJ) position papers, supplied the evidence-based clinical actions. The authors then organized recurring oral manifestations into five clinically recognizable phenotypes, paired each phenotype with chronology, host modifiers, and competing local causes, and linked a provisional working attribution with functional severity to propose the triage pathways and the two management matrices. This integration and the qualitative category definitions below are the authors' interpretive synthesis rather than a prospectively derived or validated prediction rule.

2.2. Clinical scope and specific contribution

The framework applies to patients receiving precision-oncology regimens in which conventional chemotherapy, corticosteroids, antimicrobials, radiotherapy, or bone-modifying agents often coexist: these exposures are included as competing diagnoses or effect modifiers, not reclassified as molecularly targeted treatments. Unlike drug-by-drug toxicity algorithms, the starting point is the observed oral finding, followed by a transparent consideration of alternative or concurrent explanations and functional consequences. The intended contribution is a cross-treatment communication and reassessment

pathway, not a replacement for agent-specific dosing instructions, validated grading systems, or specialist-guideline recommendations.

3. Oral adverse drug reactions as a diagnostic and pharmacovigilance problem

3.1. Phenotypic convergence in polypharmacy

Modern cancer regimens create phenotypic convergence: several mechanisms produce a limited repertoire of visible oral responses. Immune dysregulation can generate lichenoid, erosive, or aphthous-like lesions; inhibition of epithelial pathways can produce stomatitis and impaired repair; salivary dysfunction predisposes to candidiasis and mucosal trauma; antiangiogenic exposure delays healing; and antiresorptive therapy modifies the biological response of jawbone to infection and surgery. In combination regimens, these mechanisms may coexist rather than compete.[3-5]

Polypharmacy also changes the meaning of apparently minor findings. Xerostomia may be related to immunotherapy, opioid use, antidepressants, dehydration, or previous radiotherapy. A white-red lesion may represent candidiasis superimposed on lichenoid inflammation. An ulcer may be traumatic at onset but persist because of vascular impairment or neutropenia. A non-healing socket may reflect infection, antiangiogenic exposure, antiresorptive therapy, or several of these factors simultaneously. Causality should therefore be treated as graded confidence rather than a binary label.[7,11,12]

A practical mixed-causation example is a patient receiving an immune checkpoint inhibitor (ICI) and a targeted agent who develops oral erosions after a recent antibiotic course. Reticular changes at sites remote from dental contact may support an immune-inflammatory component, whereas removable plaques or a positive fungal assessment may establish simultaneous candidiasis. Treating the infection, correcting trauma, and documenting lesion-specific response can clarify the relative contributions without prematurely suspending either anticancer agent. Similarly, in a patient exposed to an antiresorptive and an antiangiogenic agent, a painful non-healing socket calls for assessment of local infection and cumulative systemic exposure. Therefore, it may be misleading to designate one drug as the sole cause in every patient.[5,6,12] These recurring phenotype clusters and their principal clinical triggers are summarized in Figure 1, providing a rapid visual guide to the phenotype-first reasoning developed in the following sections.

3.2. The limits of broad toxicity labels

Terms such as oral mucositis, stomatitis, oral pain, and dry mouth are valuable for trial reporting, but they can conceal clinically important heterogeneity. Classic oral mucositis is a dynamic biological process involving tissue injury, inflammatory amplification, ulceration, and healing. By contrast, mechanistic target of rapamycin (mTOR) inhibitor-associated stomatitis often presents as discrete aphthous-like ulcers, ICI-associated disease may be lichenoid or immune-mediated, and targeted agents may produce mixed epithelial and salivary toxicity. Applying one label to all of these entities risks applying the wrong preventive or therapeutic strategy.[13-16]

A similar limitation applies to severity grading. Lesion size does not always predict clinical burden: a small ulcer on the lateral tongue can prevent eating, while extensive reticular lichenoid change may be asymptomatic. Functional consequences such as reduced oral intake, sleep disturbance, inability to wear a prosthesis, or difficulty maintaining oral hygiene should therefore be documented alongside morphology. Patient-reported outcomes are particularly important for dryness, taste alteration, and pain, which may be substantial even when visible signs are limited.[7,9,10]

3.3. Timing, response, and causality confidence

Chronology remains a central element of attribution, but its interpretation must be treatment-specific. Cytotoxic mucositis often follows a relatively reproducible cycle, whereas immune-related oral disease can occur after variable latency and occasionally after therapy has been stopped. Targeted-therapy stomatitis may occur early and recur with subsequent cycles, while antiresorptive-related jaw complications usually reflect cumulative exposure combined with a local trigger. A credible timeline should include all anticancer drugs, supportive medications, steroid courses, antimicrobial use, blood-count abnormalities, dental procedures, and previous radiotherapy.[6,8,17]

Response to intervention can strengthen or weaken the working diagnosis. Resolution after removal of a traumatic factor argues for a local cause, although delayed healing may still indicate systemic contribution. Improvement with topical corticosteroids may support an inflammatory phenotype but does not prove drug causality. Dechallenge or rechallenge may provide useful information when these occur for oncologic reasons, yet deliberate interruption solely to test causality is often inappropriate. The clinical objective is not to achieve abstract certainty, but to reach sufficient confidence for a safe management decision.[1,18]

3.4. Limitations of rigid causality scoring

General adverse-reaction causality approaches can

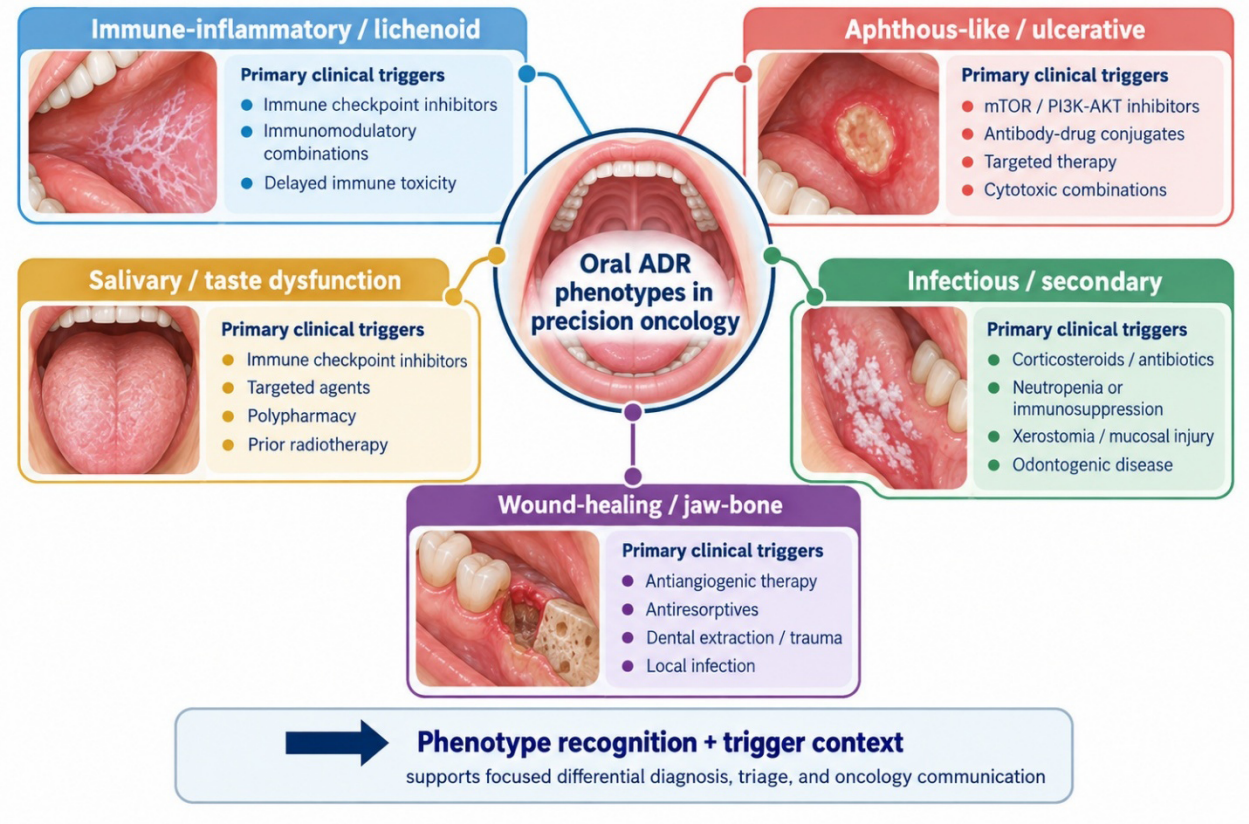


Figure 1. Conceptual map of the five core oral adverse drug reaction (ADR) phenotypes in precision oncology and their principal clinical triggers. The schematic links immune-inflammatory/lichenoid, aphthous-like/ulcerative, salivary/taste dysfunction, infectious/secondary, and wound-healing/jawbone phenotypes with common trigger contexts to support focused differential diagnosis, triage, and oncology communication.
Abbreviations: AKT: Protein kinase B; mTOR: Mechanistic target of rapamycin; PI3K: Phosphoinositide 3-kinase.

improve discipline by forcing the clinician to consider timing, alternative explanations, and response after drug withdrawal. In oncology, however, a rigid score can create false precision. Rechallenge may be unsafe or clinically unjustified, dechallenge may coincide with several simultaneous interventions, and delayed immune toxicity may not follow conventional latency assumptions. Moreover, an oral lesion often has a local co-cause—trauma, infection, or salivary dysfunction—that does not exclude a pharmacological contribution.[1,18]

For these reasons, the proposed framework uses explicit clinical reasoning rather than a single numerical threshold. The clinician records which elements support causality, which findings argue against it, what uncertainty remains, and how that uncertainty affects immediate risk. This approach is particularly important for MRONJ and other cumulative toxicities, where the relevant question is rarely whether one drug acted alone, but whether treatment exposure materially altered the response to dental infection, trauma, or surgery.[8,19]

Operationally, clinicians should document five attribution elements at the first assessment: (i) a drug–phenotype association described in credible literature; (ii) exposure-to-onset timing compatible with that agent, including delayed or cumulative toxicity; (iii) evidence for competing local or systemic diagnoses; (iv) objective findings or targeted tests when appropriate; and (v) evolution after correction of local factors, treatment of infection, or changes in anticancer exposure made for clinical, not diagnostic, reasons. Record each element as supporting, opposing, or not yet assessable, plus the reason; this qualitative checklist aims to make reasoning auditable without implying a validated numerical probability.[1,18,20]

Proposed working categories are defined as follows. “Probable” requires compatible phenotype and chronology, a reasonable exclusion or satisfactory control of major alternatives, and supportive longitudinal or objective evidence; it does not require an ethically unjustified drug rechallenge. “Plausible” requires phenotype and chronology consistent with drug toxicity but retains an

unresolved co-cause or incomplete follow-up. "Uncertain" applies when a critical element such as timing, diagnosis, or competing exposure is unknown, or when evidence genuinely conflicts. "Unlikely" applies when timing is incompatible, a better-supported diagnosis adequately explains the lesion, or the course contradicts the proposed drug association. These categories express documented clinical confidence, not formal adverse-event probability estimates or treatment grades.[1,20]

For example, a patient develops an oral lichenoid lesion three months after starting checkpoint inhibition and also has a poorly fitting prosthesis. A lichenoid biopsy pattern identifies the tissue reaction but does not identify the drug as its cause; improvement with topical corticosteroid treatment while the checkpoint inhibitor continues is likewise non-specific. The initial attribution is therefore "plausible" if the temporal association is compatible, but prosthetic trauma remains an active alternative. If removing the prosthetic trigger leads to durable complete resolution, the local explanation gains weight; if lesions persist or recur away from the contact site despite correcting trauma, drug attribution may strengthen. The case should not be called "probable" solely on histology or corticosteroid response.[21-23]

Figure 2 summarizes this reasoning. Four domains—phenotype, exposure chronology, host modifiers, and local alternatives—converge on an integrated causality assessment. The output is not simply "drug related" or "not drug related"; it is a risk category that determines whether observation, targeted testing, or urgent interdisciplinary action is required.

4. A phenotype-first clinical assessment

4.1. Immune-inflammatory and lichenoid phenotypes

Immune-inflammatory oral ADRs include reticular, plaque-like, erythematous, erosive, and ulcerative lichenoid patterns, sometimes accompanied by desquamative gingivitis or extra-oral immune-related disease. The clinical resemblance to idiopathic oral lichen planus is often close, but distribution may be less symmetrical, and onset may coincide with checkpoint blockade or another immunomodulatory therapy. Symptoms range from minimal burning to severe pain, bleeding, and impaired intake.[6,17,21,24]

The phenotype should prompt a structured differential diagnosis rather than automatic attribution to immunotherapy. Oral lichenoid drug reactions, contact reactions, candidiasis, lupus-like disease, autoimmune blistering disorders, oral potentially malignant disorders, and early squamous cell carcinoma may share white-red or erosive features. Biopsy is particularly important for unilateral, indurated, verrucous, persistently ulcerated, or treatment-refractory lesions, because lichenoid

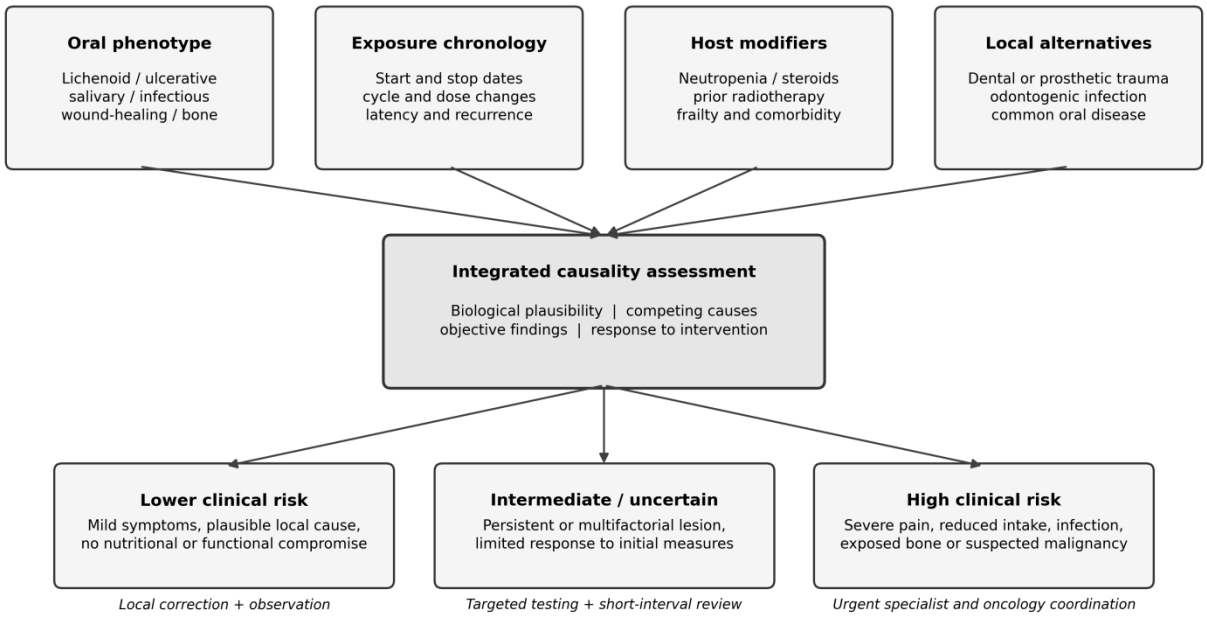


Figure 2. Phenotype-first attribution of an oral adverse drug reaction. Oral morphology is interpreted together with treatment chronology, host modifiers, and competing local causes. The resulting causality confidence is combined with clinical severity to determine observation, targeted testing, or urgent specialist and oncology coordination.

histopathology is supportive but not specific for a drug-related mechanism.[25-27]

For mild symptomatic disease, removing local irritants and using topical anti-inflammatory therapy may be sufficient. More extensive erosive disease requires closer follow-up, assessment for secondary candidiasis, and communication with oncology. Systemic immunosuppression or interruption of an ICI should be reserved for severe or refractory disease and should never be initiated as an isolated dental decision.

Clinical comparison should distinguish bilateral, relatively symmetrical idiopathic oral lichen planus from a new asymmetric or contact-site lichenoid eruption after drug exposure, while acknowledging substantial overlap: neither pattern is diagnostic alone. Interface mucositis with basal vacuolar change and a band-like lymphocytic infiltrate may occur in both conditions; eosinophils, a deeper or perivascular infiltrate, or an atypical distribution may raise suspicion of a drug reaction but lack sufficient specificity to establish causality. Direct immunofluorescence may be necessary when pemphigoid or another immunobullous condition is considered.[22,25,28]

Biopsy is most consequential when the appearance is unilateral, indurated, verrucous, persistently erosive, proliferative, or otherwise suspicious for dysplasia/carcinoma, when blistering disease enters the differential, or when an atypical lesion fails appropriate local treatment. Select a representative active margin and request histopathology with further studies if clinically indicated. A biopsy may exclude malignancy or a blistering disorder and guide treatment intensity, but a report of "lichenoid mucositis" must not itself be read as proof that the ICI caused the lesion.[25-27]

4.2. Aphthous-like, ulcerative, and stomatitis phenotypes

Ulcerative oral ADRs are clinically diverse. mTOR inhibitors characteristically produce painful aphthous-like lesions, whereas other targeted agents, antibody–drug conjugates, and ICIs may cause diffuse soreness, superficial erosions, or mixed mucositis-like disease. Because ulceration is a final common pathway, the visible lesion alone rarely identifies the responsible agent. Size, number, distribution, depth, recurrence, and relation to the treatment cycle should all be recorded.[5,16,29]

Alternative causes include mechanical trauma, recurrent aphthous stomatitis, herpes simplex virus, cytomegalovirus in immunosuppressed patients, neutropenic ulceration, candidal superinfection, and malignancy. A focal ulcer adjacent to a sharp cusp should be reviewed after elimination of trauma; a deep necrotic ulcer or one persisting beyond an expected healing interval requires a lower threshold for biopsy, viral testing, or imaging. Repeated empirical treatment without diagnostic reassessment is particularly unsafe in patients with cancer.[2,11,13]

Therapeutic context can nevertheless guide early care. For everolimus-associated stomatitis, prophylactic or early topical corticosteroid mouthwash has been studied, although evidence does not support a single universal protocol for all patients or all agents. Drug-specific recommendations are also emerging for antibody–drug conjugates with prominent stomatitis risk, reinforcing the need to identify the exact agent rather than relying on the generic label "targeted therapy."[30-32]

A superficial, typical aphthous-like ulcer with preserved oral intake, no fever or concerning focal features can receive an agent-appropriate local regimen and a documented short-interval reassessment. Atypical distribution, extensive pseudomembranes, profound neutropenia, vesiculo-ulceration, fever, or immunosuppression warrants targeted evaluation for fungal, herpesvirus, or other infectious disease according to appearance and risk. An ulcer that enlarges, is indurated or deeply necrotic, recurs at one fixed site, or persists after correction of trauma and an adequate observation interval requires expedited specialist assessment and biopsy when malignancy or another tissue diagnosis cannot be excluded. No uniform time threshold should postpone biopsy in a clinically suspicious lesion.[11,13,26,33]

It is useful to separate discrete mTOR-associated aphthous-like stomatitis from broader epithelial mucositis: prevention and topical corticosteroid evidence from everolimus or a particular antibody–drug conjugate should not be extrapolated automatically to other agents. The drug name, onset relative to dosing, neutrophil count, nutritional impact, and treatment response should be communicated together, with oncologic dose changes reserved for agent-specific protocols and shared clinical decisions.[16,29,32,34]

4.3. Salivary, taste, and neurosensory phenotypes

Xerostomia, objective hyposalivation, dysgeusia, burning, and oral dysesthesia may be the dominant oral ADR even in the absence of visible ulceration. Saliva is essential for lubrication, swallowing, speech, buffering, antimicrobial defense, and protection of dental tissues. Reduced salivary function therefore amplifies the consequences of otherwise modest mucosal disease and increases the likelihood of candidiasis, caries, denture intolerance, and traumatic ulceration.[2,7]

The diagnostic task is to separate treatment-

related salivary injury from common co-contributors. Medication burden, dehydration, anxiety, diabetes, opioid or anticholinergic use, previous radiotherapy, and oral infection should be reviewed. Subjective dryness and measured salivary hypofunction are related but not interchangeable, and both should be documented when clinically feasible. Taste alteration should be asked directly because it may reduce appetite and nutritional intake while remaining invisible during examination.[7,17,35]

Management is usually multimodal: hydration, avoidance of irritants, saliva substitutes or stimulants when appropriate, high-fluoride preventive care, candidiasis control, dietary adaptation, and review of modifiable xerogenic medications. Persistent dysesthesia without clear mucosal disease may require consideration of neuropathic pain, nutritional deficiency, or systemic causes rather than repeated antifungal or corticosteroid therapy.

Mechanisms should guide classification. ICI-associated sicca may reflect immune-mediated salivary-gland inflammation and can arise with other extra-oral immune adverse events; anticholinergic and opioid-associated dryness reflects medication effects on salivary secretion; radiation-related gland injury depends on irradiated tissue and dose; dehydration or hyperglycemia may exacerbate several mechanisms simultaneously. These processes are not interchangeable, and subjective xerostomia may occur without measurable gland hypofunction. Medication and radiotherapy history, oral dryness score, stimulated or unstimulated salivary flow when feasible, dental and candidal findings, and associated ocular or systemic symptoms should be recorded.[7,36-38]

Management is mechanism-specific in addition to symptom-oriented: review modifiable xerogenic drugs with the prescribing team, correct dehydration and treat candidiasis, institute fluoride-based caries prevention and salivary substitutes, and consider salivary stimulants only when residual function and contraindications permit. New severe ICI-associated sicca or concurrent extra-oral immune findings merits oncology assessment; suspected post-radiotherapy injury requires a distinct preventive and supportive strategy. Dysgeusia should prompt medication, oral-infection, dietary, and nutritional review rather than being assumed to represent gland hypofunction; neuropathic burning without lesions warrants assessment for non-mucosal pain mechanisms.[39-42]

4.4. Infectious and secondary phenotypes

Infection may be the primary diagnosis, a complication of treatment toxicity, or a factor that sustains an inflammatory lesion. Candidiasis is favored by xerostomia, topical or systemic corticosteroids, antibiotics, mucosal injury, and immunosuppression. Viral ulceration becomes more relevant in patients with profound immune compromise, while periodontal and endodontic infections may progress rapidly when neutrophil function or tissue repair is impaired. The presence of an anticancer drug does not eliminate the need for conventional oral infectious diagnosis.[2,11,13]

Clinical clues include removable plaques, diffuse erythematous soreness, angular cheilitis, clustered vesiculo-ulcerative lesions, necrosis, purulence, and tooth-related pain. Testing should be selective and hypothesis-driven: fungal sampling when the appearance or response is atypical, viral testing for deep or persistent ulcers in immunosuppressed patients, and dental imaging for suspected odontogenic disease. Treatment should address both the organism and the predisposing condition; otherwise recurrence is likely.

4.5. Wound-healing and jawbone phenotypes

Delayed closure of a traumatic ulcer, non-healing extraction socket, exposed bone, fistula probing to bone, unexplained jaw pain, swelling, or sensory change constitute a separate high-risk phenotype. Antiangiogenic agents can impair vascular repair, whereas antiresorptives suppress bone remodeling; combined exposure, local infection, and surgery may create additive vulnerability. These events require a broader diagnostic frame than routine postoperative healing.[8,12,19]

Medication-related osteonecrosis of the jaw must be differentiated from osteoradionecrosis, chronic osteomyelitis, periodontal or periapical disease, and jaw metastasis. Panoramic imaging may provide an initial overview, but cone-beam computed tomography or computed tomography (CT) may be needed to define sequestration, cortical destruction, or extension. Biopsy is appropriate when malignancy cannot be excluded, while indiscriminate biopsy of clearly necrotic bone may add trauma without diagnostic benefit.[43-48]

Risk assessment for MRONJ should explicitly record the cancer versus osteoporosis indication; the precise antiresorptive and route, dose intensity, duration, and cumulative exposure; previous sequential treatment with zoledronate and denosumab; concurrent antiangiogenic therapy and corticosteroids; and active periodontal or periapical infection, tooth extraction, and prosthetic pressure. Oncologic-dose therapy and combined/sequential exposures may entail different risk profiles from osteoporosis-dose treatment, although an individual numerical risk cannot be assigned from these descriptors alone. Do not use a low-risk label to dismiss new fistula, pain, or sensory change in a previously exposed patient.[19,43,49,50]

Clinical staging guides management but requires integration with imaging and the patient's goals. At-risk patients benefit from prevention and surveillance; limited exposed bone without progressive symptoms may permit hygiene measures, infection control, and close follow-up; painful, infected, or progressive disease needs maxillofacial assessment for medical and/or surgical treatment. Advanced disease with extensive destruction, fracture, extraoral fistula, or function-limiting infection requires urgent multidisciplinary planning. Stage-specific actions should follow the current position papers rather than the authors' simplified matrix alone. A normal mucosal surface does not exclude early radiographic disease or a non-exposed presentation.[51-54]

Imaging is selected to answer an oral or jaw-specific question. Panoramic radiography offers an overview, whereas CT or cone-beam CT delineates sclerosis, sequestra, and cortical spread when the extent of disease affects intervention. Magnetic resonance imaging (MRI) may characterize marrow and adjacent soft tissue in selected patients. Positron emission tomography (PET)/CT, PET/MRI, or other molecular imaging can depict metabolic activity in specialized or research contexts but do not independently establish drug causality or replace examination, conventional imaging, and histology when malignancy is suspected.[55,56] More broadly, multimodality imaging can combine nuclear-medicine and non-radioactive techniques to integrate complementary molecular and anatomic information in precision-medicine settings. Such integration is intended to exploit the distinct strengths of different modalities rather than rely on a single imaging signal.[57] Experimental dual-modality imaging can also compare target-specific and non-specific tracers within the same tumor model. In a preclinical near-infrared fluorescence/Cerenkov study, Zhang *et al.*[58] observed higher tumor uptake with non-specific immunoglobulin G than with programmed death-ligand 1 (PD-L1)-targeted atezolizumab, illustrating that target specificity alone does not determine imaging performance.

Table 1 translates the phenotype-first approach into a compact diagnostic map. It is intended to help clinicians select the minimum useful work-up and the first management priority, rather than to replace specialist judgment.

5. From suspicion to attribution: A structured workflow

5.1. Define phenotype and functional impact

The first step is to describe what is present before deciding why. Documentation should include site, distribution, color, surface, depth, symmetry, exposed bone, salivary appearance, dental or prosthetic trauma, and infection signs. Standardized photographs are valuable for comparison, particularly when treatment is remote, or

Table 1. Phenotype-first diagnostic map for suspected oral adverse drug reactions

Dominant phenotype	Common oncologic contexts	Key alternatives / minimum work-up	Immediate priority
White-red/Lichenoid	ICI; immune-modulating combinations	OLP/OLL, candidiasis, autoimmune disease, OPMD; biopsy if unilateral, indurated, verrucous, or persistent	Remove irritants; topical anti-inflammatory care; reassess and biopsy/referral when atypical
Aphthous-like/ Ulcerative	mTOR/PI3K-AKT inhibitors; ICI; ADC; cytotoxic combinations	Trauma, aphthae, HSV/CMV, neutropenia, malignancy; targeted microbiology or biopsy	Pain control, maintain intake, treat infection, short-interval review
Dry mouth/Taste change	ICI; targeted agents; polypharmacy; prior radiotherapy	Medication burden, dehydration, diabetes, candidiasis; symptom and salivary assessment	Hydration, salivary support, fluoride prevention, infection control
Infectious/ Superinfected	Steroids, antibiotics, neutropenia, salivary dysfunction	Candidiasis, viral disease, periodontal/ endodontic infection; microbiology and dental imaging as indicated	Treat organism and predisposing factor; assess systemic risk
Delayed healing/ Exposed bone	Antiangiogenic therapy; antiresorptives; combined regimens	Trauma, odontogenic infection, osteoradionecrosis, osteomyelitis, metastasis; imaging +/– biopsy	Urgent risk assessment, infection control, specialist and oncology coordination
Pain or burning with minimal signs	Targeted therapy; xerostomia; prolonged supportive medications	Neuropathic pain, candidiasis, deficiency, parafunction, dental disease	Avoid repeated empirical therapy; define functional impact and investigate selectively

Note: This matrix synthesizes contemporary oral supportive-care and oral medicine principles.[5-8]

Abbreviations: ADC: Antibody–drug conjugate; AKT: Protein kinase B; CMV: Cytomegalovirus; HSV: Herpes simplex virus; ICI: Immune checkpoint inhibitor; mTOR: Mechanistic target of rapamycin; OLL: Oral lichenoid lesion; OLP: Oral lichen planus; OPMD: Oral potentially malignant disorder; PI3K: Phosphoinositide 3-kinase.

lesions fluctuate between cycles. The record should also state what the patient cannot do because of the lesion: eat normally, swallow tablets, sleep, wear a denture, brush teeth, or maintain hydration.[9,10]

This functional layer prevents the common error of equating a visually small lesion with low clinical significance. It also provides the oncology team with information that can be incorporated into treatment decisions. Pain score, dietary modification, weight trajectory, and need for analgesics can be more clinically informative than the diameter of an ulcer alone.

5.2. Reconstruct the complete exposure timeline

A causality history should list generic drug names, not only brand names, and should include start and stop dates, cycle number, dose changes, recent holds, combination partners, and supportive medications. Previous episodes and their relationship to earlier cycles are particularly informative. The timeline should also include dental procedures, infections, antibiotic or corticosteroid exposure, neutropenia, and radiotherapy, because these factors may explain onset or modify persistence.[1,3,6]

The objective is to identify a biologically plausible window rather than to demand an immediate temporal relationship. Delayed immune toxicity, cumulative antiresorptive risk, and early targeted-therapy stomatitis follow different temporal patterns. A standardized medication chronology also makes subsequent pharmacovigilance reporting more useful.

5.3. Exclude competing causes proportionately

Diagnostic testing should be driven by the consequences of being wrong. A typical mild lesion that resolves after local correction may not require biopsy. A persistent unilateral lesion, deep ulcer, unexplained bone change, or sensory deficit has a higher diagnostic cost and justifies earlier imaging, microbiology, or tissue sampling. The threshold should be lower in patients with prior oral cancer, potentially malignant disorders, or metastatic disease.[25-27]

Dental assessment is often decisive. Pulp vitality, periodontal probing, percussion, prosthetic fit, and periapical imaging can distinguish odontogenic disease from a systemic toxicity phenotype. Similarly, candidiasis should be considered when topical corticosteroids appear ineffective, and a viral cause should be investigated when ulcer morphology, immune status, or clinical course is atypical. A drug-related explanation and a local diagnosis can coexist.[2,11,13]

When more than one cause is plausible, assign evidence to each lesion component rather than forcing a single patient-level label: photograph each site, describe whether it lies against a prosthetic edge, record microbiology when indicated, and re-evaluate after a focused intervention. An established local cause does not automatically exclude a concurrent systemic contribution to delayed healing; however, a compatible drug exposure must not substitute for investigating a persistent ulcer, unexplained numbness, or suspected malignancy.[1,26,33]

5.4. Assign working causality and reassess

The final attribution should be expressed as a working level of confidence—for example, plausible, probable, uncertain, or unlikely—together with the reasons supporting that judgment. Important supporting elements are a compatible phenotype, credible timing, lack of a stronger alternative, biological plausibility, and improvement after appropriate intervention. Persistent uncertainty is acceptable when it is explicitly documented and paired with a safe follow-up plan.[1]

Reassessment is not an administrative afterthought; it is part of diagnosis. Improvement after antifungal therapy, local trauma correction, or topical corticosteroids changes the probability of competing hypotheses. Recurrence with a later cycle may strengthen drug attribution, whereas progression despite apparently appropriate treatment should trigger reconsideration, additional testing, or specialist referral.

At reassessment, the same five domains and the functional trajectory should be re-recorded, together with the intervention performed and the duration of follow-up. If two clinicians disagree, record which domain drives the difference, for example, whether trauma is considered sufficient to explain the entire lesion, and agree on a test or review point that could resolve it. No category in this proposed framework has yet been tested for inter-rater agreement, sensitivity, specificity, or prediction of safe treatment continuation.[1,20,59]

6. Management designed to preserve treatment continuity

6.1. Universal supportive measures

Across phenotypes, several measures reduce secondary injury: non-traumatic oral hygiene, management of sharp teeth and unstable prostheses, bland rinses, avoidance of alcohol-containing mouthwashes, adequate hydration, nutritional support, and early treatment of dental infection. These measures are not substitutes for diagnosis, but they reduce microbial and mechanical amplification while the cause is clarified.[11,13]

Patient education should specify which symptoms warrant prompt contact: new ulcers, rapidly increasing

pain, inability to eat or drink, dry mouth with oral plaques, bleeding, swelling, exposed bone, non-healing sockets, or altered sensation. A written contact pathway is particularly useful for patients receiving prolonged oral targeted therapy, because low-grade symptoms may otherwise be normalized until they become functionally significant.

6.2. Phenotype-directed local treatment

Topical corticosteroids are central for many inflammatory lichenoid and aphthous-like reactions, but formulation and intensity should match site and severity. Antifungal therapy is required when candidiasis is present and may be considered during prolonged topical steroid use in susceptible patients. Salivary management combines hydration, substitutes or stimulants, caries prevention, and treatment of secondary infection. Analgesic strategies should preserve oral intake without masking progression that requires reassessment.[6,7,16]

Agent-specific protocols should be used when supported by evidence. Dexamethasone mouthwash can reduce early everolimus-associated stomatitis in selected settings, although the balance between universal prophylaxis and treatment at symptom onset remains regimen- and patient-dependent. Emerging antibody–drug conjugate protocols similarly illustrate the value of drug-specific counseling and early oral monitoring.[30-32]

6.3. Escalation and oncology communication

Oncology communication is required when symptoms reduce intake, require systemic therapy, suggest an immune-related adverse event, progress despite local care, or raise concern for infection, malignancy, or bone necrosis. The oral report should be actionable: phenotype, severity, diagnostic certainty, tests performed, current intervention, response, and whether treatment continuation appears safe from the oral perspective. General statements such as "severe stomatitis" are less useful than a concise clinical synthesis.[6,18]

The oral clinician should not independently stop an anticancer drug or recommend systemic immunosuppression without shared discussion. Conversely, oncology should not defer all oral decisions to dentistry when drug timing, disease control, and systemic immune status are essential to the risk-benefit balance. Treatment continuity is best protected through early communication before symptoms become a crisis.

Treatment continuity is a goal conditional on patient safety, not an obligation to continue despite serious toxicity. Persistent inability to eat or hydrate, rapidly progressive ulceration or infection, fever with neutropenia, suspected malignant transformation, threatened airway, clinically consequential hemorrhage, or destructive jaw disease can outweigh the benefit of uninterrupted anticancer dosing. Oral medicine should promptly document function, objective severity, diagnostic uncertainty, and local options; oncology then weighs cancer control, concurrent organ toxicities, available alternatives, and the risks of holding or modifying the specific regimen. Local corticosteroids must not delay investigation of infection or malignancy.[6,18,60]

6.4. Dental procedures during high-risk therapy

Invasive dental procedures require special planning during antiangiogenic or oncologic-dose antiresorptive therapy. Conservative restorative, endodontic, and periodontal approaches are preferred when they can predictably control infection. When extraction is unavoidable, indication, drug exposure, cancer status, blood counts, concurrent steroids, antiangiogenic therapy, and postoperative follow-up should be documented. Decisions about a drug holiday belong to the oncology–dentistry discussion because evidence is inconsistent and interruption may compromise skeletal protection.[8,19,43]

Pre-treatment dental evaluation reduces preventable risk by identifying hopeless teeth, active periodontal or endodontic infection, traumatic dentures, and planned surgery before cumulative exposure increases. However, dental clearance should not create inappropriate delays in urgent cancer care; the objective is risk reduction within the available therapeutic window. Long-term surveillance remains necessary because MRONJ may arise after prolonged exposure or local trauma.[61-63]

A preventive or therapeutic "drug holiday" must not be described as one practice across different indications and agents. For oncologic-dose antiresorptives used to prevent skeletal events, interruption can remove a meaningful therapeutic benefit and has uncertain value in preventing MRONJ; the prolonged skeletal retention of bisphosphonates further limits inference from a short pause. Denosumab has different pharmacokinetics and interruption may create other skeletal risks, particularly when prescribed for osteoporosis. Evidence from non-randomized studies and pooled analyses remains heterogeneous, while professional position statements do not uniformly agree on routine suspension. Document the indication, agent, dose, duration, urgency of dental intervention, and oncologist/prescriber's decision; do not institute a holiday solely to "prove" causation.[64-66]

Table 2 combines clinical severity and diagnostic certainty to define the appropriate level of oral treatment, oncology communication, and follow-up. Its purpose is to prevent both unnecessary escalation of mild reversible events and delayed referral of high-risk disease.

Table 2. Severity-certainty matrix for management and escalation of suspected oral adverse drug reactions

Clinical state	Oral medicine/Dental action	Oncology communication	Reassessment and reporting
Mild, clear local cause, normal function	Correct trauma or dental cause; supportive care; document baseline photograph	Routine update if systemic therapy is relevant	Review in 1–2 weeks or sooner if progression
Mild-moderate, probable ADR, diagnosis secure	Phenotype-directed local therapy; infection prevention; patient education	Inform oncology; no automatic treatment interruption	Short-interval review; record response and recurrence by cycle
Moderate, multifactorial or uncertain	Targeted microbiology, salivary testing, dental imaging or biopsy as indicated	Direct discussion if intake, adherence or systemic treatment may be affected	Reassess after defined diagnostic or therapeutic trial
Severe, rapidly progressive or function limiting	Urgent specialist assessment; analgesia, hydration/nutrition support; treat infection	Same-day oncology communication; consider systemic management or treatment modification jointly	Document outcome, dechallenge/rechallenge information and safety report
Exposed bone, non-healing socket, fistula or sensory change	Imaging, infection control, MRONJ/ORN/metastasis differential; maxillofacial referral	Urgent review of antiresorptive/antiangiogenic exposure and cancer status	Stage and follow longitudinally; record healing and oncologic consequences

Note: Escalation should reflect both clinical burden and diagnostic uncertainty.[6,8,18,19]
Abbreviations: ADR: Adverse drug reaction; MRONJ: Medication-related osteonecrosis of the jaw; ORN: Osteoradionecrosis.

7. High-risk therapeutic scenarios

7.1. Immune checkpoint inhibitors

Checkpoint inhibition is a high-risk scenario for attribution because oral immune-related adverse events may be delayed, coexist with extra-oral toxicity, and resemble familiar inflammatory diseases. Lichenoid reactions, ulceration, sicca-like dysfunction, and dysgeusia are the principal clinical patterns, but none is pathognomonic. The presence of concurrent skin, ocular, salivary, or gastrointestinal immune-related disease can strengthen an immune-mediated interpretation, while candidiasis and local trauma remain common modifiers.[6,17,21]

Management should remain severity-based. Mild localized disease is often controlled with topical therapy and close review without interrupting immunotherapy. Extensive erosive disease, inability to maintain intake, refractory salivary dysfunction, or suspicion of a systemic immune-related process requires oncology involvement and may justify systemic corticosteroids or another immunomodulatory strategy. The decision must consider cancer response and other organ toxicities.[6,18]

Before systemic immunosuppression or an ICI hold is contemplated, jointly assess the total ulcerated or erosive area, pain, ability to swallow and maintain nutrition, response to adequate topical therapy, bacterial/fungal/viral infection, concurrent skin/ocular/gastrointestinal or other organ immune-related adverse events, cancer response, and alternatives to the current regimen. Limited stable mucosal disease with adequate intake may be managed locally while ICI continues under observation; severe refractory erosions, a rapidly progressive immune process, or significant extraoral immune-related adverse events justify urgent oncology-led reassessment of systemic treatment. Rechallenge decisions should be individualized after documented improvement and should not be represented by the dental team as automatic.[6,18,36,60]

7.2. Pathway-targeted agents and antibody–drug conjugates

Targeted therapies are a high-risk scenario for under-recognition because low-grade oral symptoms can persist across months of treatment. The clinician should distinguish aphthous-like mTOR inhibitor-associated stomatitis from diffuse cytotoxic mucositis and from candidal or traumatic ulcers. Early intervention is important because pain may become dose-limiting before lesions appear extensive, and recurrent symptoms can lead to patient-driven dose omission.[3,16,29]

Antibody–drug conjugates further broaden the phenotype. Drug-specific stomatitis prophylaxis and monitoring recommendations are emerging, but extrapolation across agents is unsafe because targets and payloads differ. The medication history should therefore include the exact antibody–drug conjugate, treatment cycle, prophylactic regimen, and concurrent therapy. Oral services need mechanisms for rapid updating as new agents enter practice.[5,32]

7.3. Antiangiogenic and antiresorptive combinations

Combination therapy can change both the mechanism and the diagnostic yield of the lesion. For example, an ICI may contribute to lichenoid inflammation, a targeted

agent may weaken mucosal recovery, and corticosteroid exposure may permit candidal superinfection; treating only one component may leave the patient symptomatic. For antibody–drug conjugate-related stomatitis, report the exact conjugate and payload context, concurrent medications, current cycle, and any prophylaxis rather than applying a generic class algorithm. A single-cycle recurrence is supportive but not diagnostic if accompanying drugs change.[5,6,32,67]

Combined antiangiogenic and antiresorptive exposure is high risk because soft-tissue repair and bone remodeling may be impaired simultaneously. Local infection, extraction, or prosthetic trauma can then become the trigger for delayed closure, bone exposure, or MRONJ. Risk is not uniform, but the threshold for pre-treatment dental stabilization, conservative care, and close postoperative surveillance should be lower than in patients without these exposures.[8,12,43]

Once bone exposure or a fistula probing to bone occurs, management is individualized according to stage, infection, pain, cancer prognosis, and patient preference. Conservative care remains appropriate for selected early or medically fragile cases, while persistent symptomatic or progressive disease may benefit from surgical management. The goal is disease control and quality of life rather than passive observation of exposed bone.[19,68,69]

Sequential zoledronate–denosumab exposure, simultaneous antiresorptive/antiangiogenic therapy, and local infection can act as cumulative or interacting contributors. When the socket fails to heal, clinicians should evaluate odontogenic infection, osseous imaging, prior radiation, and possible tumor involvement, and document each relevant exposure; attributing failure to the last drug started may be misleading. The regimen should be modified only after stage, symptoms, oncologic indication, and patient preferences have been reviewed with the prescribing oncologist and maxillofacial team.[19,49,50]

8. Documentation, patient-reported outcomes, and pharmacovigilance

An isolated oral event becomes clinically useful evidence only when it is documented in a reproducible form. A minimum dataset should include the suspected drug and cycle, other relevant medications, lesion phenotype and site, onset, severity, functional impact, photographs, competing diagnoses, tests, treatment, response, and whether the anticancer regimen was continued, modified, or stopped. This structure improves communication and enables meaningful comparison across patients.[1,9]

Patient-reported outcomes should be integrated rather than treated as optional. Pain, dry mouth, taste change, difficulty eating, and sleep disturbance are experienced continuously by patients but sampled intermittently by clinicians. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) development and validation demonstrate the value of structured patient reporting for symptomatic adverse events, and the same principle is highly relevant to oral toxicity, where clinical signs may underestimate burden.[9,10,70]

Pharmacovigilance also requires outcome data. Reporting a lesion without documenting resolution, recurrence, dechallenge, rechallenge, or treatment consequence limits causal interpretation. Oral medicine follow-up can add this missing temporal information and can identify whether an intervention preserved cancer-treatment continuity. The result is a learning system rather than a collection of isolated case descriptions.

A brief recurring patient-reported checklist should capture pain, oral dryness, taste change, oral intake, swallowing, hygiene, and sleep at baseline and at each clinically relevant treatment interval. Patient reporting complements rather than replaces morphology, objective investigation, and oncologist assessment; use the same questions over time so worsening function triggers earlier contact before unsupervised dose omissions. These items are a proposed oral surveillance subset, not a newly validated oral-specific instrument. [9,10,71,72]

Figure 3 illustrates this clinical-to-pharmacovigilance cycle. Detection leads to characterization, attribution, action, and reassessment; structured reporting then feeds back into counseling, preventive protocols, and earlier referral. The minimum dataset is the link between individual care and collective knowledge.

9. Research priorities

The first priority is a more precise oral toxicity vocabulary. Oncology trials should distinguish diffuse mucositis from aphthous-like stomatitis, lichenoid disease, salivary dysfunction, infection, and wound-healing or bone complications. Core morphological descriptors and a minimum oral dataset would improve comparability without requiring every trial site to provide specialist oral medicine diagnosis.[5-7]

Second, clinical studies should link professional grading with patient-reported function. Pain, dryness, and dysgeusia need longitudinal measurement, while nutrition, oral hygiene, and treatment adherence should be captured as consequences rather than assumed from lesion grade. This would clarify which apparently low-grade events are

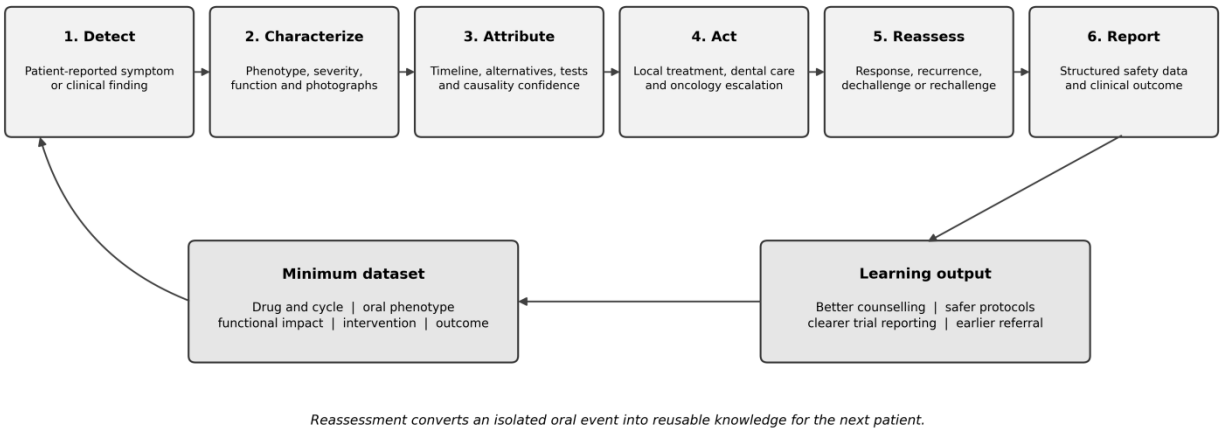


Figure 3. Clinical-to-pharmacovigilance learning cycle for oral adverse drug reactions. The pathway emphasizes that detection alone is insufficient: characterization, attribution, intervention, reassessment, and structured reporting are all needed to transform an individual event into safer future care.

most likely to threaten treatment continuity.[9,10,70]

Third, preventive strategies require prospective validation in therapy-specific populations. Evidence supporting dental evaluation before bone-modifying therapy is stronger than evidence for many other oral pathways, and even here implementation is inconsistent. Similar prospective models are needed for checkpoint-inhibitor oral screening, targeted-therapy stomatitis prevention, and oral monitoring for new antibody–drug conjugates.[30,32,62,63]

Finally, combination regimens should be studied as combinations rather than as isolated drug exposures. Registries should record cumulative antiresorptive and antiangiogenic therapy, steroid use, radiotherapy, dental infection, and invasive procedures. Such data are essential for risk models that reflect real-world oncology and for defining when conservative dental care, surgery, or treatment modification produces the best patient-centered outcome.[43,44,68]

9.1. Limitations of the proposed framework

Phenotype-first reasoning can be unreliable in atypical, rapidly changing, or multi-lesion presentations; in profoundly immunocompromised patients, the same ulcer can reflect infection, trauma, neutropenia, and drug injury. Oral phenotype is not a substitute for tissue diagnosis of suspected cancer, microbiological testing in high-risk infection, imaging of destructive bone disease, or organ-specific immune-toxicity grading. Temporal exposure may remain inseparable in fixed combination regimens, and improvement after corticosteroids or local correction does not establish a unique cause. The model has not undergone prospective validation or inter-rater reliability testing; category thresholds and proposed management matrices are expert synthesis intended to prompt documentation and referral, not prescriptive clinical guidelines.

Moreover, different lesions in the same patient may have distinct or overlapping etiologies so that a single patient-level causality label may obscure clinically important differences between sites. In these settings, lesion-specific documentation, targeted microbiological or histopathological investigation when indicated, and short-interval reassessment are preferable to forcing a unified attribution.

Future work should prospectively test agreement between clinicians assigning the proposed working categories, ideally across different levels of oral-medicine expertise and using standardized clinical documentation. Because a definitive reference standard for drug causality will often be unavailable, adjudication procedures will be needed for discordant or unresolved cases, while validation cohorts should include heterogeneous combination regimens and changes in immune status over time. Validation should assess not only category concordance but also whether framework-guided triage improves clinically relevant outcomes, including timely diagnosis, symptom control, nutritional status, and avoidance of unnecessary anticancer-treatment interruption. Trials of agent-specific prophylaxis, imaging-guided MRONJ planning, and stage-adapted surgical versus conservative care should be interpreted in their particular therapeutic populations rather than generalized to all oral ADRs. Patient-reported symptoms and follow-up after both continued and interrupted treatments are needed to test the proposed benefit of coordinated care.

10. Conclusion

Oral ADRs in precision oncology are not adequately managed by memorizing lists of drug-specific toxicities. The clinically decisive task is to determine what phenotype is present, how severely it affects function, whether the treatment timeline is plausible, which local or systemic alternatives remain, and what degree of certainty is sufficient for action. A phenotype-first approach makes this reasoning explicit and helps clinicians avoid both over-attribution and diagnostic delay.

Most mild and reversible oral events can be managed with local therapy, infection control, salivary support, and close review while effective cancer treatment continues. Severe, persistent, atypical, function-limiting, or bone-related findings require earlier specialist assessment and direct oncology communication. Structured follow-up and patient-reported outcomes complete the process by showing whether the intervention worked and whether treatment continuity was preserved.

Embedding oral medicine within pharmacovigilance transforms the mouth from a peripheral toxicity site into a meaningful source of safety information. The proposed figures and tables provide a practical framework for that transition: from lesion recognition to causality confidence, from uncertainty to proportionate escalation, and from an individual adverse event to better preventive care for future patients.

These recommendations are a narrative, unvalidated clinical synthesis: unusual morphology, immunosuppression, concurrent drug toxicities, possible malignancy, and destructive bone disease require standard diagnostic escalation, even when the suggested phenotype appears familiar. When attribution cannot be resolved, explicitly documenting the uncertainty and coordinating a safety-led oncologic decision is preferable to either automatic continuation or automatic discontinuation.

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