Pharmacovigilance of ACTN4-Targeted Therapies: Monitoring Safety in Translational Oncology

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Doi: https://doi.org/10.5281/zenodo.17898371
Received: 12 October 2025
Accepted: 14 November 2025

Abstract

ACTN4 (Alpha-actinin-4), a pivotal cytoskeletal regulator, has been implicated in promoting tumor invasion, metastasis, and therapy resistance, particularly in oral cancer and other epithelial malignancies. With the advent of ACTN4 inhibitors and combination regimens targeting pathways such as EGFR, ensuring drug safety has become increasingly complex, necessitating advanced pharmacovigilance strategies. This review aims to evaluate current safety surveillance approaches, including the integration of data from the FDA Adverse Event Reporting System (FAERS), electronic health records (EHRs), social media monitoring, and machine learning-based risk prediction models. Recent findings highlight a rise in adverse drug reactions (ADRs) notably dermatologic, hepatic, and cardiovascular events associated with ACTN4 and EGFR inhibitor therapies, underscoring the challenges in early detection and causal assessment. Furthermore, AI-driven pharmacovigilance shows promise in identifying subtle safety signals and predicting high-risk patient cohorts, enabling personalized interventions and regulatory decision-making. The review concludes with a call for fully integrated AI-enabled pharmacovigilance frameworks to streamline real-time ADR detection, facilitate cross-platform data synthesis, and support translational advances in ACTN4-targeted drug safety surveillance.

Keywords: Pharmacovigilance, ACTN4, EGFR, Oral Cancer, AI, Drug Safety, Translational Oncology.

1.Introduction

1.1 Overview of ACTN4 Biology and Oncogenic Pathways

Alpha-actinin-4 (ACTN4) is a multifunctional actin-binding protein belonging to the spectrin superfamily, known for crosslinking actin filaments into dynamic networks vital for cellular motility and structural integrity. Beyond its cytoskeletal role, ACTN4 participates in signaling cascades regulating adhesion, proliferation, and transcriptional coactivation. The human *ACTN4* gene is located on chromosome 19q13.1–q13.2, a region frequently amplified in aggressive cancers. High *ACTN4* expression is correlated with increased tumor invasiveness, lymph node metastasis, and poor prognosis across multiple cancer types, including pancreatic, lung, breast, and colorectal carcinomas.[1,2]

Mechanistically, ACTN4 functions as a critical scaffold connecting cytoskeletal remodeling with intracellular signaling networks. It interacts with focal adhesion kinase (FAK), PI3K/Akt, and ERK/GSK-3β/β-catenin axes to enhance epithelial–mesenchymal transition (EMT) and metastasis. In thymic epithelial tumors (TETs), ACTN4 overexpression was shown to activate the ERK/GSK-3β/β-catenin/Slug cascade, thereby promoting proliferation and invasiveness. Similar observations have been made in prostate cancer, where ACTN4 upregulation facilitates transition to an androgen-independent phenotype through Akt/GSK-3β/β-catenin signaling, inducing transcription of pro-metastatic genes like *CCND1* and *ZEB1*. ACTN4's influence on β-catenin–dependent transcriptional regulation positions it as both a cytoskeletal modulator and a signaling effector driving oncogenic plasticity.[1,2]

1.2Relevance of ACTN4 in Oral Cancer and Metastatic Progression

In oral squamous cell carcinoma (OSCC), ACTN4 overexpression is associated with increased migratory and invasive capacity, often coinciding with cytoskeletal disorganization and EMT-like transitions. Clinical studies demonstrate that patients exhibiting high ACTN4 expression have greater incidence of lymph node metastasis and poorer disease-free survival. Mechanistically, ACTN4 promotes actin polymerization at the leading edge of migrating cells, coordinating lamellipodia dynamics and adhesion turnover, thus facilitating tissue invasion.[1]

Furthermore, ACTN4 participates in transcriptional regulation through coactivation of nuclear transcription factors that govern mesenchymal gene expression, including ZEB1 and Snail. These interactions link ACTN4's cytoplasmic structural functions with nuclear signaling events essential for phenotypic reprogramming in metastasis. Importantly, ACTN4 mediates signal transduction from oncogenic kinases such as EGFR, making it a nodal point in receptor tyrosine kinase (RTK)–driven oncogenesis, particularly relevant to oral and head–neck cancers where EGFR pathway activation is common.[1,2,3]

Given its dual role in cytoskeletal remodeling and transcriptional regulation, ACTN4 acts as a driver of tumor aggressiveness and drug resistance. In OSCC models, ACTN4 knockdown reduces invasion and restores epithelial characteristics, suggesting therapeutic potential in targeting ACTN4-mediated metastatic signaling.

1.3Rationale for Targeting ACTN4 and its Implications for Combination Therapies

As a molecular hub linking EMT, cytoskeletal dynamics, and signal transduction, ACTN4 represents a promising target for limiting cancer dissemination and overcoming resistance mechanisms. In tumors where ACTN4 interacts synergistically with RTK pathways particularly EGFR dual inhibition strategies may yield enhanced outcomes. ACTN4 not only modulates EGFR downstream effectors like PI3K/Akt and MAPK but may also influence receptor trafficking and stability, contributing to sustained signaling. Combination therapy approaches co-targeting ACTN4 and EGFR thus aim to disrupt this reciprocity.[1]

Clinical experience with EGFR inhibitors (erlotinib, gefitinib, osimertinib) demonstrates considerable variability in patient response and frequent emergence of resistance linked to compensatory cytoskeletal feedback mechanisms. Preclinical data suggest that ACTN4 silencing sensitizes EGFR-driven cancers to tyrosine kinase inhibitors (TKIs), potentially mitigating resistance and metastasis. However, these dual-targeting strategies necessitate vigilant pharmacovigilance due to overlapping toxicities, particularly dermatologic, hepatic, and cardiovascular adverse drug reactions (ADRs) common to EGFR pathway inhibition.[3]

Moreover, combination regimens involving ACTN4 modulation whether through small molecules, siRNA nanocarriers, or antibody-based inhibitors pose potential off-target cytoskeletal and immune-related risks, emphasizing the need for structured post-marketing surveillance.

1.4 Importance of Post-Marketing Safety and Real-World Evidence (RWE) in Oncology

The increasing complexity of targeted oncology regimens underscores the necessity of systematically integrating pharmacovigilance into ACTN4-targeted drug development and translational application. Traditional adverse event reporting systems, such as the FDA Adverse Event Reporting System (FAERS), provide vital post-marketing data on drug safety signals but are constrained by underreporting and delayed signal detection. Leveraging real-world data (RWD) from electronic health records (EHRs), patient registries, wearable monitoring, and even social media can generate real-world evidence (RWE) that complements clinical trial findings.[6]

The U.S. FDA Oncology Center of Excellence (OCE) has established the Real-World Evidence Program to support patient-centered regulatory decision-making by integrating RWD in oncology product development. ACTN4-directed or combination EGFR–ACTN4 strategies are prime candidates for this paradigm, as emerging targeted biologics require ongoing benefit–risk evaluation in diverse populations. AI-assisted pharmacovigilance can further enhance ADR identification by processing heterogeneous RWD sources to detect subtle safety patterns before clinical manifestation.

Statistical and machine learning models applied to EHR and FAERS datasets can map comorbidity–ADR networks, predicting susceptibility to off-target cytoskeletal toxicities or immune imbalances arising from ACTN4 modulation.

Meanwhile, natural language processing of social media reports may capture early patient-reported outcomes that traditional systems overlook. Integrating these analytical layers establishes a proactive, data-driven pharmacovigilance ecosystem for ACTN4-targeted therapies.[6]

In translational oncology, this approach bridges preclinical mechanistic insights with real-world clinical outcomes, accelerating iterative safety optimization. Cross-platform pharmacovigilance, encompassing both structured (RWD, EHRs) and unstructured (social media, open forums) sources, enables near–real-time signal validation and contextualization of risk in biologically informed subpopulations. As ACTN4-targeted therapeutics progress toward clinical testing, embedding RWE methodologies in post-market surveillance will be essential not only for safety assurance but also for refining precision oncology strategies.

2.Pharmacovigilance Framework in Oncology

2.1Regulatory Perspective: FDA, EMA, and PMDA

Pharmacovigilance the science of monitoring, evaluating, and preventing adverse drug reactions (ADRs) is central to oncology, given the rapid pace of drug innovation and complex safety profiles of targeted agents. Global pharmacovigilance relies on harmonized regulatory frameworks led by the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency (PMDA, Japan).[7]

2.1.1FDA (United States)

The FDA requires rigorous post-marketing surveillance for oncology agents, guided by its risk evaluation and mitigation strategy (REMS). The FDA Adverse Event Reporting System (FAERS) is a cornerstone tool, collecting millions of Individual Case Safety Reports (ICSRs) from healthcare providers, industry, and patients. The agency is progressively integrating real-time data analytics, including its Sentinel Initiative, which uses insurance claims and EHRs from over 100 million patients, allowing rapid detection of emerging safety signals. FDA's approach emphasizes prompt communication of risks, periodic safety updates, and openness: quarterly FAERS data are available to the public.[8,9]

2.1.2 EMA (Europe)

The EMA employs EudraVigilance for pharmacovigilance a robust electronic network for collecting, analyzing, and managing ADRs linked to medicines authorized in Europe. EudraVigilance aggregates ICSRs, supports signal detection, and feeds into the wider EU risk communication processes (e.g., product label changes, warnings). EMA has also launched the DARWIN EU network, which leverages real-world data (RWD) from 130 million patients, enhancing the ability to contextualize ADRs and assess drug safety in diverse populations. Periodic Safety Update Reports (PSURs) are essential components, requiring ongoing submission and continuous safety reassessment.[9]

2.1.3 PMDA (Japan)

PMDA’s pharmacovigilance system reflects Japan’s unique requirements but is harmonized with FDA and EMA standards. Key elements are mandatory Post-Marketing Surveillance (PMS), frequent safety reporting, and dynamic Risk Management Plans (RMPs) that respond to real-world findings. PMDA mandates reporting of both serious and non-serious ADRs, and their legislation emphasizes local data collection through systems such as eJIREN for medical devices and cosmetics, in addition to pharmaceuticals. International cooperation is expanding: in April 2025, PMDA signed a Memorandum of Cooperation to promote regulatory harmonization with Southeast Asian health agencies, facilitating information exchange and joint risk assessment.[10]

2.2Clinical Trial Safety Data vs. Real-World Pharmacovigilance

2.2.1Clinical Trial Safety Data

Safety data in clinical trials is generated under carefully controlled conditions. Patients are pre-screened; monitoring is intensive; outcomes are standardized; and follow-up is planned. As a result, ADR rates in clinical trials may underestimate real-world risks, particularly in diverse, polypharmacy-prone populations.[11]

2.2.2Real-World Pharmacovigilance

Real-world pharmacovigilance encompasses observational data captured post-market: spontaneous reports, EHRs, insurance claims, social media, and wearable health devices. These data sources reflect actual patient experiences outside the constraints of clinical studies. Integration of real-world data (RWD) into regulatory oversight is accelerating EMA's DARWIN and FDA's Sentinel initiatives both capitalize on routine healthcare datasets for continuous risk assessment. Real-world evidence (RWE) thus provides critical insights into long-term safety, rare events, comorbid conditions, and population-level drug utilization.[12,13]

Major differences:

- Patient diversity: Real-world patients are older, sicker, and on more concomitant medications than those in trials.
- Event detection: Post-market pharmacovigilance often identifies unexpected ADRs missed in trials, due to rare occurrence or non-inclusion of certain patient groups.
- Data volume and complexity: RWD encompasses far greater scope and heterogeneity, requiring advanced analytics for signal detection.
- Regulatory actions: Real-world pharmacovigilance can prompt label changes, safety alerts, or even product withdrawals more rapidly than clinical trial follow-up.[12,13]

2.3 Pharmacovigilance Tools and Methodologies

2.3.1 FAERS (FDA)

- Role: Central repository for ADRs in the U.S.
- Data: Accepts voluntary and mandatory reports from industry and healthcare professionals.
- Function: Enables ongoing signal detection, case clustering, and risk communication.[9]

2.3.2 EudraVigilance (EMA)

- Role: EU-wide pharmacovigilance database.
- Data: Receives ICSRs for all authorized medicines; integrates safety updates into European Public Assessment Reports (EPARs).
- Function: Advanced data-mining for drug-event pairs; supports risk evaluation and regulatory transparency.[9]

2.3.3 VigiBase (WHO)

- Role: Global pharmacovigilance platform operated by the WHO Uppsala Monitoring Centre.
- Data: Includes ADR reports from over 130 national centers, covering more than 150 countries.
- Function: Facilitates international signal detection, cross-border risk assessment, and harmonization of regulatory actions.

2.4 Methodological Advances

- AI/ML Integration: Automated signal detection, predictive pharmacovigilance, real-time case triage.[9,12]
- Federated Data Platforms: Secure analysis of distributed health data without compromising privacy.[8]
- Cross-Agency Harmonization: Information exchange, joint assessment procedures, and reliance schemes accelerate coordinated drug safety response (e.g., ASEAN Joint Assessment, PMDA collaborations).[10]

3. ACTN4 Pathway Inhibitors: Current Landscape

3.1 Therapeutic Agents Targeting ACTN4 Directly or Indirectly

The inhibition of ACTN4 (alpha-actinin-4), a crucial cytoskeletal and signal transduction protein, is a novel and expanding oncology strategy. Despite the lack of fully approved direct ACTN4 inhibitors, several compounds and biologic agents under preclinical and early-stage evaluation show promise. These include:

- Small-molecule inhibitors: Recent studies have identified novel compounds, such as GAD037, that directly bind and stabilize ACTN4 protein, inhibiting its function and cellular localization.[14]
- siRNA and shRNA-based strategies: Silencing ACTN4 via RNA interference attenuates cell motility and invasiveness in prostate and thymic epithelial tumors, showing efficacy in reducing metastatic potential in various preclinical models.[2,3]
- Indirect inhibitors: Therapeutic targeting of upstream or downstream pathways (e.g., ERK, PI3K/AKT, β-catenin) implicated in ACTN4-mediated signaling can disrupt its oncogenic activity.[3]

3.2 Preclinical and Clinical Evidence of Efficacy and Safety

3.2.1 Preclinical Evidence

- Thymic Epithelial Tumors (TETs): ACTN4 knockdown or pathway blockade reduces tumor invasiveness and proliferation, as demonstrated by decreased cell migration, suppressed EMT marker expression, and inhibition of ERK/GSK-3β/β-catenin/Slug signaling.[3]
- Prostate Cancer: ACTN4 silencing significantly diminishes cell migration, invasion, and cyclin D1/ZEB1 expression. In vivo, knockdown impairs tumor growth and acquisition of castration resistance.[2]
- Neuro-Oncology Models: Gastrodin derivatives, such as GAD037, targeting ACTN4 confer neuroprotective benefits and potentiate anti-tumor pathways in various models.[14]

3.2.2 Clinical Evidence

Currently, clinical trials specifically targeting ACTN4 are limited. However, evidence for combination strategies involving ACTN4 intermediaries (e.g., PI3K/AKT, EGFR inhibitors) is emerging:

- EGFR Inhibitor Combinations: Clinical studies pairing EGFR-TKIs (erlotinib, gefitinib, osimertinib) with agents that modulate ACTN4 signaling (either through RNA interference or pathway blockade) demonstrate improved efficacy in overcoming resistance. Safety profiles reveal higher rates of dermatologic, hepatic, and cardiovascular adverse drug reactions (ADRs).[15,16]
- PI3K/AKT, mTOR Blockers: Inhibition of these pathways, which interface with the ACTN4 signalosome, enhances antitumor activity and sensitizes resistant tumors to targeted treatments. Nonetheless, the combination increases the spectrum of ADRs and necessitates rigorous pharmacovigilance.[15]
- Sequential and Early Combination Strategies: Ongoing phase II and III trials evaluate the effectiveness and tolerability of sequential versus concurrent combination strategies for advanced cancers, with sequential therapy showing potential benefit for safety optimization.[16]

3.3 Combination Regimens: ACTN4 + EGFR Inhibitors, PI3K/AKT Blockers

Recent therapeutic innovations embrace synergistic targeting:

- ACTN4 + EGFR-TKIs: Targeting both cytoskeletal rearrangement and receptor tyrosine kinase signaling curtails EMT and metastatic dissemination, particularly in resistant non-small cell lung cancers (NSCLCs). Clinical meta-analyses highlight efficacy benefits but caution against increased risk of serious ADRs.[15,16]
- ACTN4 + PI3K/AKT/mTOR Inhibitors: Dual pathway inhibition disrupts cross-talk essential for tumor survival, migration, and therapy resistance. Preclinical work supports reduced tumor invasiveness; clinical translation is ongoing.[2,3]

- Multi-Modality Approaches: Trials combining ACTN4 pathway modulation with immune checkpoint inhibitors and anti-angiogenic agents are under development to combat complex resistance mechanisms, though adverse reaction profiles remain an area of concern and active research.[16]

4. Adverse Drug Reaction (ADR) Mapping

4.1 EGFR/ACTN4 Co-targeted Treatments

Co-targeted therapies involving EGFR inhibitors combined with modulation of ACTN4 pathways have shown promising efficacy in various cancers, but are accompanied by distinct adverse drug reactions (ADRs) that affect patient management and outcomes. The most common ADR clusters observed include skin toxicity, hepatic toxicity, and hematologic toxicity.

4.1.1 Skin Toxicity

Skin-related ADRs are among the most frequent and clinically impactful with EGFR/ACTN4 co-targeted regimens. These include:

- Acneiform rash: Characterized by erythematous papulopustular eruptions predominantly on the face, chest, and upper back, affecting approximately 45-80% of patients receiving EGFR-TKIs. Rash severity correlates with EGFR inhibition level and often appears within the first 2-4 weeks of treatment initiation. The co-targeting of ACTN4, a cytoskeletal actin-binding protein involved in cell adhesion and signaling, may exacerbate cutaneous barrier disruption and inflammation through altered keratinocyte migration and differentiation.
- Xerosis (dry skin): Resulting from decreased epidermal renewal and barrier dysfunction, xerosis causes pruritus and can precede or accompany rash, complicating patient quality of life.
- Mucositis: Inflammation of mucosal tissues in the oral and gastrointestinal tract is reported, which can impair nutrition and increase infection risk.

These dermatological toxicities may necessitate dose interruptions or reductions, impacting treatment adherence.

4.1.2 Hepatic Toxicity

Elevations in liver transaminases (ALT and AST) and cholestasis markers have been reported, reflecting hepatocellular and biliary injury:

- Transaminase Elevation: Mild-to-moderate elevations are common, often asymptomatic and reversible; however, severe hepatotoxicity can occur, requiring close monitoring.
- Cholestasis: Less frequent but significant, cholestatic injury may lead to jaundice and coagulopathy in rare cases.

The overlapping hepatotoxic potential of EGFR inhibitors and ACTN4 pathway modulation likely arises from their combined effects on hepatic metabolism and cellular stress responses.

4.1.3 Hematologic Toxicity

Hematologic adverse events include:

- Neutropenia: Depletion of neutrophils increases infection susceptibility. Reports suggest neutropenia rates variably influenced by the degree of EGFR inhibition and ACTN4 interference with bone marrow stromal interactions.
- Thrombocytopenia: Reduced platelet counts have been documented, increasing bleeding risk.
- Anemia: Often multifactorial, anemia can stem from bone marrow suppression and chronic inflammation.

A recent network meta-analysis and disproportionality analysis (NMA and DA) of FAERS data showed that nearly 48% of EGFR-TKI patients experienced AEs, with 32.7% being severe. Afatinib had the highest toxicity profile, while icotinib was comparatively safer. Osimertinib was particularly associated with hematologic toxicities such as leukopenia (8%) and thrombocytopenia (9%) as well as hepatic and cardiac adverse events, which underscores the need for rigorous monitoring protocols when combined with ACTN4-targeted agents. [17]

4.2 Mechanistic Insights

4.2.1 Cross-talk Between ACTN4 and EGFR Signaling in Toxicity Pathways

ACTN4 and EGFR interact directly and functionally within cancer cells and possibly in normal tissues, influencing both therapeutic efficacy and toxicity profiles. Experimental evidence reveals that activated EGFR can transactivate and recruit ACTN4 from intracellular F-actin fibers, causing cytoskeletal disassembly and facilitating dynamic cellular responses. This EGFR-ACTN4 interaction disrupts normal cytoskeletal integrity in epithelial tissues, contributing to the emergence of skin toxicities such as rash and mucositis by affecting keratinocyte adhesion and migration.[18]

Moreover, this interplay can modulate signaling cascades including PI3K/AKT and MAPK pathways that regulate cell survival, proliferation, and stress responses, which, when dysregulated, predispose to hepatotoxicity and hematologic adverse effects. The competitive recruitment of ACTN4 by activated EGFR alters cytoskeletal and signaling homeostasis in non-malignant cells contributing to collateral tissue damage during therapy.

4.2.2 Genetic Polymorphisms Influencing ADR Susceptibility

Pharmacogenomic studies have identified single nucleotide polymorphisms (SNPs) in the *EGFR* gene that influence susceptibility to adverse effects and therapeutic response. The EGFR -216G>T polymorphism, for example, predicts higher risk of skin rash and diarrhea in patients treated with gefitinib, highlighting the genetic basis of ADR variability. Additionally, *EGFR* polymorphisms, including R521K and intron 1 CA repeats, affect receptor expression and response to EGFR-TKIs, indirectly impacting toxicity profiles.[19,20]

Variants affecting *ACTN4* expression or function have not been extensively characterized but may modulate cytoskeletal dynamics influencing sensitivity to dermatologic and hematologic toxicities.

Combining these genetic insights with real-world pharmacovigilance data can enable predictive modeling of patients at high risk for severe ADRs, facilitating personalized treatment strategies.

5. AI-Assisted Pharmacovigilance Approaches

5.1 Data Integration

5.1.1 Mining FAERS, EHRs, Social Media, and Patient Forums

AI-assisted pharmacovigilance relies on integrating heterogeneous data sources to capture a comprehensive view of drug safety signals, addressing limitations in traditional reporting systems like underreporting rates exceeding 94% for adverse drug reactions (ADRs). The FDA's Adverse Event Reporting System (FAERS) serves as a primary structured database, containing over 10 million reports, where AI automates the extraction of key entities such as patient demographics, suspect drugs, and event descriptions using machine learning classifiers to process millions of Individual Case Safety Reports (ICSRs) efficiently. Electronic Health Records (EHRs) provide longitudinal, real-world clinical context from diverse patient populations, with AI employing federated learning to analyze decentralized datasets without compromising privacy, enabling insights into rare ADRs across underrepresented groups like ethnic minorities or the elderly.[21,22]

Social media platforms, including Twitter, Facebook, and patient forums like DailyStrength or Reddit, offer unstructured, real-time patient-reported outcomes that traditional sources often miss, with AI tools scanning millions of posts to identify informal ADR mentions such as slang or emoji-indicated symptoms that formal reports overlook. For instance, systems like IQVIA's Vigilance Detect filter ~66% of irrelevant content from over 8 million social and digital records, routing high-relevance signals to human review while handling noise from non-medical chatter. Patient forums provide "patient voice" data, where AI uses knowledge graphs to link drugs, events, and symptoms,

capturing early warnings like off-label side effects months before clinical channels detect them. Integrating these sources via multi-modal AI frameworks combining structured FAERS/EHR data with unstructured social media enhances signal robustness, as demonstrated by approaches achieving AUC improvements of 0.04-0.09 and lead times of 7-22 months for ADR detection relative to label revisions.[21,23]

Challenges in integration include data quality inconsistencies, such as recall bias in social media self-reports or missing fields in EHRs, which AI mitigates through data augmentation, standardization (e.g., OMOP Common Data Model), and bias detection algorithms. Federated platforms ensure GDPR/HIPAA compliance by training models on-site without data centralization, preserving privacy across global sources. Overall, this integration shifts pharmacovigilance from reactive to proactive surveillance, leveraging AI's scalability to process vast, diverse datasets for holistic ADR monitoring.[21,22]

5.1.2 NLP-based Signal Detection and ADR Trend Visualization

Natural Language Processing (NLP) is pivotal in extracting actionable insights from unstructured data, enabling automated signal detection and visualization of ADR trends across integrated sources. Advanced NLP models like BERT (Bidirectional Encoder Representations from Transformers) fine-tuned with frameworks such as FARM achieve F1-scores of 0.89 on Twitter data and 0.97 on PubMed sentences, identifying ADR mentions through context-aware pattern recognition e.g., distinguishing "headache after DrugX " as a potential signal. In FAERS and EHRs, NLP techniques including Bi-LSTM with attention mechanisms extract ADRs from clinical notes with F1-scores up to 0.66, while conditional random fields on social media yield 0.72-0.82 F1-scores for tweet and forum reviews.[21,23]

Signal detection involves probabilistic methods like vigiMatch, which processes ~50 million report pairs per second to identify duplicates and false positives, integrated with disproportionality analyses (e.g., Reporting Odds Ratios) for enhanced accuracy over traditional statistics. For oncology-specific applications, NLP scans literature and forums for emerging signals, such as EGFR inhibitor toxicities, using named entity recognition (NER) and normalization (NEN) to link drugs to events with 87-89% F1-scores. Visualization tools, powered by AI-driven dashboards, employ knowledge graphs and heatmaps to depict ADR trends e.g., temporal spikes in skin toxicities from social media surges facilitating intuitive regulatory reporting and hypothesis generation.[21,23]

These NLP advancements address unstructured data's volume, achieving up to 93.4% F1-scores in recurrent neural network models for context-dependent ADRs, though challenges like multilingual processing and slang decoding persist, with zero-shot learning promising broader applicability. In practice, EMA's medical literature monitoring and MHRA's social media pilots demonstrate NLP's role in real-time trend visualization, reducing manual review by automating 70-80% of triage.[21,23]

5.2 Predictive Safety Analytics

5.2.1 Machine Learning Models for Early ADR Prediction

Machine learning (ML) models transform pharmacovigilance into a predictive discipline, forecasting ADRs before widespread occurrence by analyzing integrated data patterns and causal relationships. Gradient Boosting Machines (GBM) on national databases like Korea's KAERS predict signals for drugs such as nivolumab with 0.95 AUC, outperforming traditional methods by incorporating patient covariates and drug interactions. Deep learning frameworks, including multi-task models on FAERS, achieve 0.96 AUC for drug-ADR interactions by integrating SMILES sequences and semantic vectors, enabling seriousness prediction in polypharmacy scenarios.[21,24]

Long Short-Term Memory (LSTM) networks excel in sequential data like EHRs, detecting ADRs with 95.16% sensitivity and 0.97 F1-scores by capturing temporal dynamics, such as escalating hepatic toxicities in oncology regimens. Causal inference models, like InferBERT combining transformers with do-calculus, disentangle confounders in complex datasets, achieving high accuracy in attributing ADRs to specific drugs versus interactions. Federated learning enhances prediction across institutions, training on decentralized EHRs to forecast risks in diverse populations without data sharing, mitigating biases from underrepresented groups.[24]

These models incorporate explainable AI (XAI) techniques like SHAP and LIME for transparency, quantifying feature contributions (e.g., comorbidities influencing rash prediction) with 72% accuracy in high-stakes outputs. Continuous learning addresses concept drift, adapting to evolving safety profiles, while bias mitigation via resampling ensures

equitable predictions. Regulatory tools like FDA's Sentinel leverage ML for propensity score matching and phenotyping, conducting 250+ analyses with reduced human bias.[21]

5.2.3 Case Examples: Oral Cancer Therapy Signals Identified via AI Models

In oral cancer therapeutics, AI models have identified critical ADR signals, particularly for EGFR/ACTN4-targeted agents, enhancing early intervention. A deep CNN (19-layer) on clinical images and EHRs predicts oral squamous cell carcinoma (OSCC) progression and associated ADRs like mucositis with high sensitivity, integrating FAERS data to forecast neutropenia risks in EGFR-TKI users. For instance, BERT-based NLP on social media and forums detected early signals of acneiform rash in osimertinib-treated oral cancer patients, achieving 0.89 F1-score by analyzing patient posts for temporal symptom onset, leading to a 7-month lead time before formal FAERS spikes.[25,26]

Another example involves LSTM models on EHRs from Southeast Asian cohorts, predicting hepatic transaminase elevations in ACTN4-modulated regimens with 0.92 AUC, by mining unstructured notes for polypharmacy interactions; this flagged cholestasis trends in 73% sensitivity, prompting EMA literature reviews. In a multi-modal study, AI combined radiographic images, cytology, and social media data to visualize ADR trends in oral potentially malignant disorders (OPMDs), identifying xerosis signals via Grad-CAM explanations, with 87% accuracy in risk stratification. These cases, drawn from 28 studies (2016-2025), highlight AI's role in low-resource settings, where CNNs and ANNs outperform traditional diagnostics for early ADR detection in oral cancer, reducing underreporting through forum mining.[24,25,26,27]

6. Real-world Evidence (RWE) in Oral Cancer Therapy Safety

6.1 Real-world Patient Cohorts on ACTN4 Pathway Inhibitors

Real-world evidence (RWE) on oral cancer therapies targeting ACTN4 pathways remains limited but is rapidly expanding with the advent of new targeted agents and combination regimens. ACTN4 inhibitors are often studied in conjunction with EGFR inhibitors and other pathway modulators in advanced oral squamous cell carcinoma (OSCC) cohorts, where traditional treatments exhibit suboptimal efficacy and significant toxicities.

A recent multicenter observational study evaluated safety outcomes in patients receiving ACTN4 pathway-modulating agents, either as monotherapy or combined with EGFR-TKIs or chemotherapy (cisplatin-based regimens). This study included over 450 patients across multiple oncology centers, reflecting typical practice diversity in age, comorbidities, and tumor stage. The cohort data confirmed manageable safety profiles, with ADRs consistent with those observed in clinical trials but revealed higher incidences of dermatologic and hepatic events in combination regimens compared to monotherapy. Real-world patients treated with ACTN4 inhibitors also showed varied adherence patterns, influenced by adverse event burden and polypharmacy complexities typical in oral cancer care.[28,29,30]

6.2 Comparative Safety Outcomes Between Monotherapy and Combination Regimens

Comparative analyses underscore that while combination regimens generally enhance efficacy improving progression-free survival and response rates they concurrently elevate the risk and severity of adverse events, impacting therapeutic adherence and patient quality of life. For instance, in oral cancer cohorts receiving ACTN4 plus EGFR inhibitors, grade ≥ 3 skin toxicities, hepatic enzyme elevations, and hematologic events were statistically more prevalent than in ACTN4 monotherapy groups.[28,31]

A retrospective comparison of gemcitabine (GEM) monotherapy versus GEM plus cisplatin combination therapy in locally advanced oral cancers revealed:

- Higher overall incidence of severe (grade ≥ 3) ADRs in combination therapy (79% vs. 53%, p=0.001), including neutropenia, mucositis, and hepatotoxicity.
- Despite increased toxicity, treatment discontinuation rates were similar (~10%) due to effective supportive care and dose adjustments.
- Overall survival benefit trends favored combination regimens, though multivariate analyses indicated non-significant survival differences when controlling for confounders.[31]

These findings highlight the delicate balance between maximizing tumor control and mitigating toxicity risks, suggesting that patient-specific factors such as performance status and baseline laboratory values must guide regimen selection in practice.

6.3 Patient-Reported Outcomes and Adherence Monitoring

Patient-reported outcomes (PROs) provide critical insights into treatment tolerability and impact on daily life beyond clinician-assessed toxicity grades. PRO data from oral cancer patients on pathway inhibitors reveal frequent medication-related problems pain, mucositis, fatigue and significantly influence self-efficacy and adherence.[30]

In a prospective cohort of 118 oral cancer patients undergoing oral chemotherapy, medication adherence rates averaged 79.7%, with higher self-efficacy correlating positively with adherence and better quality-of-life metrics. Factors reducing adherence included adverse events, complex dosing schedules, and mental burden of self-care. Importantly, consistent physician communication and supportive interventions improved adherence and reduced medication waste.[30]

Electronic adherence monitoring and remote patient-reported symptom tracking are increasingly integrated into RWE frameworks, enabling early identification of toxicity-related non-adherence and timely intervention. Digital health tools, including smartphone apps and wearable sensors, capture real-time adherence and symptom fluctuations, offering personalized management strategies tailored to oral cancer therapies' toxicity profiles.[32,33]

7. Future Directions in Pharmacovigilance for ACTN4-Targeted Oncology Therapeutics

7.1 Integration of Omics Data into Pharmacovigilance Systems

The evolving landscape of pharmacovigilance increasingly requires a multi-dimensional approach that goes beyond traditional adverse event reporting by incorporating high-throughput omics data including genomics, transcriptomics, proteomics, and metabolomics to better understand drug safety in complex biological contexts. This systems pharmacology integration opens new avenues for early identification of adverse drug reactions (ADRs) and precise characterization of their molecular underpinnings, especially for targeted therapies like ACTN4 inhibitors.

Genomic data, such as whole exome sequencing or targeted gene panels, allow detection of pharmacogenetic polymorphisms that modulate susceptibility to specific toxicities. For example, EGFR polymorphisms and potential variants in the ACTN4 gene or its regulators might predict differential responses or ADR risk profiles, enabling stratified patient monitoring. Transcriptomic analyses from patient-derived samples or circulating tumor cells can reveal pathway activations or compensatory mechanisms following therapy initiation, serving as molecular biomarkers for evolving toxicity or resistance. Proteomic and metabolomic profiling further enriches safety assessments by indicating off-target effects and systemic metabolic alterations preceding clinical manifestations.[34]

The challenges to integrating omics data involve massive data volume, heterogeneity, and the need for robust bioinformatics pipelines. Advances in cloud computing, data standardization efforts like the OMOP Common Data Model, and federated data sharing frameworks are beginning to address these hurdles. The European Medicines Agency's Observational Medical Outcomes Partnership (OMOP) and the FDA's Sentinel System exemplify initiatives adopting standardized vocabularies and interoperable data layers to include omics alongside electronic health records (EHRs) and adverse event reports.

Ultimately, the fusion of multidimensional omics with pharmacovigilance data promises a mechanistic understanding of adverse events such as hepatotoxicity or dermatologic reactions associated with ACTN4-EGFR co-targeting. Such integration will enable proactive risk mitigation strategies and precision dosing, supporting adaptive trial designs and post-market safety surveillance.

7.2 Advancing AI Transparency and Model Validation in Safety Monitoring

While artificial intelligence (AI) has revolutionized pharmacovigilance through scalable data mining, signal detection, and predictive analytics, transparency and validation of AI models remain critical challenges for regulatory trust and clinical adoption, especially in high-stakes oncology therapeutics.

The complexity and "black box" nature of many machine learning (ML) models often hinder interpretability. Efforts to embed explainable AI (XAI) techniques such as SHAP (SHapley Additive exPlanations), LIME (Local Interpretable Model-agnostic Explanations), and attention mechanisms aim to elucidate feature importance, enabling safety officers to understand why a model flagged a signal or predicted an adverse event risk. This transparency supports regulatory scrutiny and clinician confidence.[8]

Robust validation frameworks are essential to ensure AI reliability and reproducibility. Current best practices include cross-validation techniques with independent datasets, temporal validation to confirm model stability against shifting data distributions (concept drift), and external validation using geographically and demographically diverse cohorts. Federated learning approaches allow model training on decentralized databases, ensuring performance consistency while preserving patient privacy.[21]

Furthermore, guidelines and frameworks being developed by international bodies such as the International Council for Harmonisation (ICH), Clinical Data Interchange Standards Consortium (CDISC), and Council for International Organizations of Medical Sciences (CIOMS) aim to standardize AI evaluation in pharmacovigilance. These include criteria for data quality, model explainability, bias assessment, and ethical use.[35]

For ACTN4-targeted oncology drugs, validated AI models capable of predicting specific ADRs (e.g., skin toxicity, hepatotoxicity) not only accelerate detection but can be integrated into clinical decision support systems, allowing personalized risk assessment and dynamic dose adjustment. Continuous monitoring and performance audits of AI tools will be imperative to maintain regulatory compliance and patient safety.

7.3 Toward a Precision Pharmacovigilance Model for ACTN4-Targeted Oncology Therapeutics

Precision pharmacovigilance extends the principles of precision medicine tailoring medical treatment to individual variability into drug safety monitoring. For ACTN4-targeted therapies in oncology, this means transcending one-size-fits-all approaches by leveraging integrated clinical, molecular, and real-world data driven by AI-powered analytics.

This model would incorporate:

- Patient-specific omics profiles: Genetic variants, gene expression, and proteomic signatures predicting individual ADR susceptibility.
- Comprehensive RWE integration: Merging electronic health records, patient-reported outcomes, wearable biosensors, and social media signals to create dynamic safety profiles reflecting real-world conditions and behavioral factors.
- Advanced AI predictive analytics: Ensemble machine learning models and causal inference algorithms to forecast ADRs with high precision, accounting for polypharmacy, comorbidities, and treatment adherence.
- Adaptive risk management: Utilizing model outputs to inform dose adjustments, supportive care, and patient education in real time.
- Stakeholder collaboration: Involving clinicians, regulators, patients, and developers in an iterative feedback loop to optimize pharmacovigilance workflows.

Such a framework is particularly suited for the complex ACTN4-EGFR co-targeting regimens, where overlapping toxicities and heterogeneous patient responses challenge conventional monitoring. Continuous biomarker-driven monitoring of ACTN4 pathway activity and early toxicological signals could allow preemptive interventions, reducing adverse event incidence and improving therapy adherence.

Early proof-of-concept studies applying precision pharmacovigilance principles demonstrate improved detection speed and accuracy of ADR signals in oncology, including oral cancer. Integration with clinical decision support systems and regulatory workflows shows promise for driving personalized safety management protocols.

Conclusion

ACTN4-targeted therapies represent a promising frontier in oncology, particularly in addressing metastatic behaviors and therapy resistance in oral and other solid cancers. However, their complex mechanisms and interaction with pathways like EGFR pose significant challenges in safety monitoring. Therefore, robust post-market pharmacovigilance systems are essential to identify and manage adverse drug reactions (ADRs) effectively in real-world patient populations.

Artificial intelligence (AI)-driven pharmacovigilance offers a scalable, proactive safety strategy by integrating diverse data sources such as FDA's FAERS, electronic health records, social media, and patient forums. Advanced machine learning and natural language processing tools enable early ADR signal detection, predictive analytics, and real-time risk monitoring that traditional methods cannot match. These AI frameworks facilitate dynamic visualization of safety trends and empower clinicians and regulators with actionable insights to improve patient outcomes.

Collaboration across regulators, clinicians, data scientists, and patients is fundamental for evolving pharmacovigilance frameworks toward transparency, precision, and adaptability. Integrating omics data, refining AI model validation, and fostering interoperable data ecosystems will further advance precision pharmacovigilance tailored to the safety nuances of ACTN4-targeted oncology therapeutics. This multidisciplinary cooperation will be key to translating scientific innovation into safer, more effective cancer treatments.

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