Literature Review: Interpretable Deep-Learning and Ensemble Models for Predicting Multidrug Resistance in Klebsiella pneumoniae

1. Introduction

Carbapenem-resistant Klebsiella pneumoniae is listed as a “critical” priority pathogen by the World Health Organization (WHO, 2024). The bacterium causes hospital infections that are increasingly hard to treat. Global genomic studies show that certain clones, such as ST258, spread quickly and carry multiple resistance genes (Wyres et al., 2020). Rising resistance and limited treatment options have turned this organism into a major clinical threat.

Machine learning (ML) offers new ways to predict resistance from genome data, but clinical use remains rare. K. pneumoniae acts as a intermediary for resistance genes, making it a good model for genomic prediction research (Navon-Venezia et al., 2017). Early reviews highlight both promise and limits of ML in antimicrobial resistance (AMR) prediction, particularly the lack of model transparency (Kim et al., 2022). This review traces how computational models evolved from rule-based systems to deep and transformer models and identifies the main barriers to clinical translation.

Despite high reported accuracies, recent benchmarking studies show that interpretability remains the biggest hurdle (Hu et al., 2024; Kim et al., 2022). The following sections examine how different modeling approaches perform and what they reveal about resistance biology.

2. The AMR Challenge in Klebsiella pneumoniae

2.1 Clinical Significance

WHO (2024) classifies carbapenem-resistant K. pneumoniae among the most dangerous pathogens for hospital-acquired infections. A global review found high rates of carbapenem-resistant isolates, especially in intensive care units (Lin, 2024). Mortality rates are often above 40%, and combined resistance to carbapenems, fluoroquinolones, and aminoglycosides leaves few treatment options.

European genomic surveillance confirmed the regional spread of carbapenemase-producing clones such as ST258 and ST512 (Budia-Silva et al., 2024; Bowers et al., 2015). These lineages carry plasmids that move easily between bacteria, speeding resistance spread. Together, these findings highlight an urgent need for genome-based surveillance and prediction.

2.2 Genomic Complexity

Population genomics shows that K. pneumoniae is highly diverse (Wyres et al., 2020). Its accessory genome varies widely, and many strains gain or lose resistance elements over time. Earlier work described this genetic mosaicism in detail (Holt et al., 2015), while Lam et al. (2021) developed Kleborate, a typing tool that links sequence types with virulence and resistance genes. Multiple resistance mechanisms such as plasmid-mediated β-lactamases, efflux pumps, and porin mutations act together to create broad resistance (Navon-Venezia et al., 2017). The wide range of ESBL plasmids further complicates prediction (Hawkey et al., 2022).

2.3 Prediction Challenges

Genome-based prediction faces several problems. Resistance often depends on combinations of genes, mobile elements, and point mutations that interact in nonlinear ways (Su et al., 2019). These complex patterns limit the value of simple rule-based methods and point toward machine learning approaches that can detect subtle relationships across genomes.

3. Evolution of Machine Learning Approaches

3.1 Traditional Methods

Earlier AMR prediction relied on detecting known resistance genes using databases such as CARD and ResFinder (Su et al., 2019; Florensa et al., 2022). These systems produced binary resistant/susceptible calls but depended on pre-defined gene lists. Their main weakness was the inability to recognize new mechanisms or capture combinations of mutations. Because of that, rule-based approaches often failed when genomes carried novel variants or incomplete gene sets.

3.2 Classical ML Era

Feature-based models became common around 2020. Ensemble methods such as XGBoost and LightGBM used engineered features like gene presence or k-mers. Yan et al. (2021) showed that LightGBM could predict complex genomic traits with high accuracy. Liu et al. (2024) applied XGBoost to identify virus-related sequences, while Joe and Kim (2024) demonstrated its use for multi-label classification that is relevant for multi-drug resistance prediction. These methods provided clear feature importance scores, giving partial interpretability.

In K. pneumoniae, Macesic et al. (2020) built one of the first ML models for polymyxin resistance using genomic data. Later studies by Condorelli et al. (2024) and Batisti Biffignandi et al. (2024) extended this to several antibiotic classes and minimum inhibitory concentration prediction. While performance improved, these models still relied on expert-defined genomic features and gave limited biological insight.

3.3 Deep Learning Emergence

The success of convolutional neural networks (CNNs) in genomics (Eraslan et al., 2019) led to new ways to learn sequence patterns directly from DNA. Zeng et al. (2016) showed CNNs could identify DNA-protein binding motifs. Later, Koo and Ploenzke (2021) improved interpretability by modifying activation functions to better capture motif structure. In AMR prediction, López-Cortés et al. (2024) introduced MSDeepAMR, which used transfer learning for resistance prediction, and Lyu et al. (2023) applied deep learning to spectral data for rapid K. pneumoniae detection. These methods boosted accuracy but often behaved as "black boxes," leaving biological meaning unclear.

3.4 Transformer Models

Transformer architectures mark the latest step. Ji et al. (2021) introduced DNABERT, treating DNA as a language to learn sequence context. Zhou et al. (2024) released DNABERT-2, a faster, multi-species version, and Dalla-Torre et al. (2025) presented the Nucleotide Transformer, trained on large human genome datasets. Transformers outperform CNNs on many genomic tasks and offer attention maps that can show which motifs or regions influence predictions. These models promise both high accuracy and interpretable sequence context.

4. Current State and Limitations

4.1 Performance Benchmarks

Hu et al. (2024) compared major ML algorithms across 78 species-antibiotic combinations. They reported F1-scores between 0.85 and 0.92 for well-studied organisms, showing that genome-based resistance prediction can match traditional testing for many pathogens. Ren et al. (2022) similarly showed high accuracy using whole-genome data and multiple algorithms. However, performance often drops when models face new data. Roberts et al. (2017) warned that random cross-validation inflates accuracy in datasets with phylogenetic or temporal structure. Nsubuga et al. (2024) found that models trained on African E.coli isolates did not generalize well across countries. Abdollahi-Arpanahi et al. (2020) compared deep learning and ensemble methods and found that ensemble approaches often matched or exceeded deep learning when data were limited. In conclusion, most studies confirm strong in-sample results but weak generalization across time or geography.

4.2 Interpretability Gap

From a clinical standpoint, explainable predictions are essential. Kim et al. (2022) emphasized that clinicians must understand why a model predicts resistance before acting on it. Regulatory approval also depends on interpretability. Recent methods address this by adding transparency layers. Dickinson and Meyer (2022) created Positional SHAP (PoSHAP) to

interpret sequence-based models. Koo et al. (2021) developed global importance analysis to quantify genomic features in deep networks, and Van Hilten et al. (2021) designed the GenNet framework for inherently interpretable architectures. Still, these methods highlight features without always linking them to biological mechanisms. Most explanations remain statistical rather than mechanistic.

4.3 Clinical Translation Barriers

Even accurate and interpretable models face hurdles in real settings. Kim et al. (2022) pointed to gaps in computational infrastructure, workflow integration, and clinician training. A meta-analysis by Tang et al. (2022) noted high development costs and uncertain cost-benefit in routine testing. Validation across time and sites is rare, leaving model reliability uncertain. The gap between research accuracy and clinical usefulness still remains wide.

5. Research Opportunities

Several gaps define the next research steps. First, interpretability remains shallow, models explain features but not mechanisms (Kim et al., 2022). Second, temporal and phylogenetic validation are limited (Roberts et al., 2017). Third, generalizability across populations is unclear (Nsubuga et al., 2024).

Future work should combine interpretable ensemble methods like XGBoost and LightGBM (Yan, 2021; Liu, 2024) with transformer models that learn sequence context (Dalla-Torre, 2025). Integrating feature importance from trees with attention weights from transformers could yield models that perform well and reveal underlying resistance signals. This approach aligns with the need for clinical-grade accuracy ($F1 \geq 0.85$) and biological interpretability (Dickinson & Meyer, 2022).

6. Conclusion

Research over the past decade shows a clear trend: from rule-based systems (Su, 2019) to deep learning and transformers (Dalla-Torre, 2025). Studies like Hu (2024) confirm that genome-based prediction can achieve high accuracy, but interpretability and clinical acceptance remain limited (Kim 2022). Given the genomic diversity of K. pneumoniae (Wyres 2020), accurate and interpretable models are essential. Ensemble-transformer hybrids that combine attention and feature importance may bridge this gap and move AMR prediction closer to clinical use.

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