DAYZERO DIAGNOSTICS

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Abstract Summary

Large-Scale Predictive AST using Machine Learning and WGS

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Background

The advent of on-demand whole genome sequencing (WGS) could revolutionize infectious disease diagnostics through the analysis of pathogen DNA. Antimicrobial susceptibility test (AST) profiles based on genomic data could be delivered in hours rather than days. While bioinformatic approaches based purely on identification of resistance markers have been shown to be insufficient for this task, machine learning (ML) offers an attractive alternative. We assessed the concordance of Keynome gAST - an ML system we developed for predicting AST results from pathogen WGS inputs - with phenotypic AST for a broad collection of bacterial isolates from a single hospital.

Methods

Between 4/20-8/12/2023, 1,303 bacterial isolates were collected by the UCI Microbiology Lab. Species ID (using MALDI-TOF) and phenotypic AST (primarily using VITEK 2 and Kirby Bauer testing) were performed for clinical care. Isolates were sequenced with Illumina. Samples not passing quality standards or with no matching ML models were removed (N=139); 18 species were analyzed. Reads were passed to Keynome gAST models that were predetermined to provide high confidence (52 species/drugs) and moderate confidence (45 species/drugs) predictions based on cross-validated performance. Of note, Keynome gAST was trained on a dataset of ~43k samples and ~439k phenotypic AST results from geographically diverse sources that include UCI. Keynome gAST predictions (S/I/R) were compared to phenotypic AST results to determine categorical agreement (CA), major error (ME), and very major error (VME) rates.

Results

Keynome gAST produced 6,258 high-confidence predictions with aggregate ME and VME rates <2% and CA >96%. A further set of 3,245 moderate-confidence predictions showed expectedly lower performance but still with CA >89% (Table 1). Good performance was demonstrated on empiric drugs with high clinical relevance such as ceftriaxone with E. coli (98.3% CA/ 0% VME/ 0.3% ME; N=419) and K. pneumoniae (99.1/0/0; N=121), imipenem with E. coli (99.2/0/0; N=417) and K. pneumoniae (97.5/0/0; N=121), and vancomycin with E. faecium (100/0/0; N=31). Models achieved an aggregate CA >94% across a broad range of additional drug classes including fluoroquinolones (9 species), aminoglycosides (5 species, including Pseudomonas aeruginosa), and sulfonamides (4 species).

Conclusion

These results demonstrate the potential of Keynome gAST to provide phenotypic-grade, categorical (S/I/R) calls from genomic data for a broad range of 97 clinically relevant species-drug combinations.