Keynome *g*AST: a machine learning system for predicting antimicrobial resistance phenotypes from whole-genome sequencing

Jason Wittenbach; Paul Knysh; Arolyn Conwil; Nicholas Worley; Samuel Nitz; Hayden Sansum; Connor Capitolo; Danielle Peterson; Defne Surujon; Matt Turner; Nicole Billings; Mohamad Sater; Miriam Huntley

Traditional antimicrobial susceptibility testing (AST) provides a direct observation of a pathogen's antimicrobial resistance/susceptibility (AMR/S) phenotype, which is a critical piece of information in targeting appropriate therapy to patients with bacterial infections. Unfortunately, these tests rely on culturing the bacteria from blood and then observing cell growth (or lack thereof).a This process can take days to complete – time which a critically ill patient may not have. Recent advances in molecular diagnostics offer a quicker turn-around based on targeted amplification of known resistance markers in the pathogen DNA. But such techniques are limited to detecting only the most well-characterized resistance markers in the most widely-studied pathogens, thus severely limiting their negative predictive value. Here we review the current state of diagnostics for bacterial bloodstream infections and present Keynome *g*AST (genomic AST) – a machine learning (ML) system for predicting AMR/S phenotype from pathogen whole-genome sequencing data derived directly from whole blood via an ultra-high pathogen DNA enrichment process. The ML models at the heart of the system are trained on MicrohmDB – our extensive database of paired pathogen genomes and traditional AST results. The models learn genomic signatures that predict AMR/S phenotype, even for species and drugs where resistance mechanisms are not yet well characterized. We show Keynome *g*AST can achieve >90% agreement with traditional AST (>95% for strongly susceptible/resistant samples) on 100 contrived direct-from-blood samples across a panel of >40 pathogen-drug combinations, and demonstrate its superiority to resistance marker based approaches.