Towards genomic prediction of drug resistance in tuberculosis

In 2014, WHO approved a new strategy for the elimination of tuberculosis, and recommended that countries adapt the strategy’s pillars—patient-centred care, supportive systems, and innovation—as appropriate to their local contexts. The need for a novel approach to elimination of tuberculosis in low-incidence settings was further echoed in a second framework that laid out eight priority areas. Among the prescribed interventions were investment in new technologies and rapid drug-susceptibility testing to optimise treatments. In The Lancet Infectious Diseases, Timothy Walker and colleagues present an important study at the nexus of these areas, establishing a foundation for routine use of whole-genome sequencing in the mycobacteriology laboratory.

With the cost of sequencing a bacterial genome now similar to that of standard bacteriological assays such as drug-susceptibility testing (Pankhurst L, Oxford University, personal communication), a new framework is emerging in clinical microbiology, for which a single sequencing run is used to both diagnose an infection and predict its antibiotic susceptibility. Whole-genome sequencing is especially appealing for the tuberculosis laboratory—resistance in Mycobacterium tuberculosis arises largely because of point mutations, and whole-genome sequencing can yield clinically actionable predictions of antibiotic susceptibility within days rather than the weeks or months of standard approaches. Ultimately, the ability to quickly predict an isolate’s drug sensitivities from genomic data will lead to faster prescribing of an appropriately tailored treatment regimen, in turn leading to a lower risk of emergent resistance and more rapid conversion to a non-infectious state, enabling a patient to resume a normal lifestyle.

The key to implementation of bespoke treatment based on whole-genome sequencing is to have a comprehensive database of resistance-associated mutations. Although some canonical mutations in genes such as inhA and rpoB bring about several drug-resistant phenotypes of tuberculosis, many other resistance mutations exist, some of which have been catalogued in databases such as TBDreamDB and MUBII-TB-DB, but many of which are unknown. Walker and colleagues present both an extended range of known resistance mutations and an algorithm to discover new mutations. In their study, they examine a large dataset of 3651 M tuberculosis genomes representing different genetic lineages, each with phenotypic results from drug-susceptibility testing. They selected 2099 isolates as a training dataset and developed an algorithm to scan for mutations in 23 genes associated with antibiotic resistance. The algorithm identified 991 mutations potentially associated with resistance; when these were combined with phenotypic data, 120 mutations ultimately emerged as being potentially predictive of resistance. Using these mutations as the basis of a classifier to predict phenotypes in the 1552 validation genomes, Walker and colleagues were able to assign nine of 10 validation cases to the correct class—sensitive or resistant—with a mean 92.3% sensitivity (95% CI 90.7–93.7) and 98.4% specificity (98.1–98.7). The investigators then re-ran the algorithm on the complete set of 3651 genomes, increasing the pool of resistance-associated mutations to 232 and improving predictive capacity—assigning 96.1% of isolates to the correct class with only a negligible decrease in specificity.

This study is an important first step towards routine genomic prediction of antibiotic susceptibility in tuberculosis. A reliable catalogue of resistance mutations is needed if whole-genome sequencing is
to be standardised and validated for use in the clinical setting, as is a protocol (such as the algorithm outlined by Walker and colleagues) that can continually be retrained to identify novel resistance-associated mutations when new genomes become available. To sustain the momentum of this approach, the community of health-care specialists in tuberculosis should commit to sharing genome sequences through public repositories, including clinical metadata such as results from drug-susceptibility testing. As sequencing moves from the research laboratory into the reference laboratory, a clash of values might occur between the open-data mindset of genomics research and public health’s inherent concern with data stewardship and privacy. However, the two communities should navigate the new landscape together to create centralised, public-facing genomic repositories containing the metadata needed to train and test new predictive tools, and maintaining patient confidentiality and addressing issues of data ownership and attribution.

Can genomics ever completely replace phenotypic-resistance testing? Perhaps not, because of many reasons—the suite of resistance-associated mutations for a specific organism might not ever be completely known; compensatory mutations can be difficult to tease out from those causing resistance; and the role of minor variants and other influences on resistance, such as expression levels, has not yet been fully described. Even so, whole-genome sequencing offers the potential of rapid first-pass phenotyping and, in a world where multidrug-resistant tuberculosis is a growing problem, an opportunity to rationally tailor treatment to individuals.

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Antibiotics, copayments, and antimicrobial resistance: investment matters

Antibiotics are unequivocally one of the greatest innovations in medicine, but the threat of resistance is approaching a tipping point. In Europe alone, health care and productivity costs are estimated at more than €1·5 billion per year,\textsuperscript{1} with costs in the USA estimated at US$55 billion.\textsuperscript{2} Accurate data from low-income and middle-income settings are insufficient.\textsuperscript{3,4} With only two new classes of antibiotics developed since the 1970s, the possibility of a world without antibiotics is a global concern. If the absence of new antibiotics and the lack of innovation continue, we are in danger of entering the post-antibiotic era, with routine and life-saving care disrupted, such as cancer chemotherapy, surgical procedures, and treatment of infection in neonates.

Innovation in new classes of antibiotics has been unattractive for the biopharmaceutical industry because new drugs would probably be used only after existing antimicrobial agents were exhausted.\textsuperscript{5,6} The Office of Health Economics published findings showing that the value of a new musculoskeletal drug can be up to 20 times higher than that of a new antibiotic to the developing pharmaceutical company.\textsuperscript{7} Clearly these figures are not aligned with disease burden and pandemic potential of resistant infections, and innovation is desperately needed.

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