Tuberculosis is Changing

This March, Public Health England will officially launch a routine whole-genome sequencing service for mycobacterial infections, becoming the first national administration in the world to do so. The implications are profound with many of the methods that have become commonplace around the world being replaced. From now on, when mycobacterial cultures are referred to reference facilities, comprehensive whole-genome sequencing-based reports will be returned within 5–7 days. Reports will detail mycobacterial species, and predict drug susceptibility and genetic relatedness for the *Mycobacterium tuberculosis* complex. The changes have the potential to affect how clinical decisions are made, and how tuberculosis control is done. Other countries are already preparing for a similar transition and will be watching events in England carefully. If all goes well, we could soon see widespread international adoption of similar procedures.

The costs of whole-genome sequencing are expected to be covered by phasing out tests currently on offer.1 These include 24-locus mycobacterial interspersed repetitive units–variable number of tandem repeat (MIRU–VNTR) typing for which whole-genome sequencing has been shown to have a greater specificity, promising savings to the public health budget by avoiding unnecessary contact investigations, and improved disease control by virtue of more focused deployment of resources.2 They also include the various line-probe assays on the market, which target short nucleotide sequences that can easily be identified in whole-genome sequencing data. Because genomic analysis allows the detection of many rarer mutations alongside the dominant ones, an increase in sensitivity over PCR-based assays is expected.3

Whole-genome sequencing is the logical conclusion of a shift away from culture methods that started with the arrival of PCR-based technologies in diagnostic microbiology. The best known direct-from-sample test is the MTB/RIF Xpert, which can identify the *M tuberculosis* complex directly from clinical samples and flag multidrug-resistant disease.4 Although whole-genome sequencing provides more complete data than this assay, culture remains a prerequisite to sequencing. However, direct whole-genome sequencing from clinical samples is looking promising and if technologies such as strand sequencing evolve as expected, there is the prospect of them taking over as first-line, definitive, culture-free assays.5 Price permitting, this would complete the shift away from culture.

The implications for clinical management are already far reaching. Clinicians will start receiving interpreted diagnostic reports based on genomic mutations, eventually cross-correlated to minimum inhibitory concentrations. If received within a useful timeframe, this information could supplant empirical therapy, with treatment tailored to the susceptibility of the

organism at initiation. It could also allow routine decisions to be made about offering higher doses to patients whose strains harbour mutations that cause only low-grade resistance (eg, upstream fabG1/inhA mutations for isoniazid).6 The precision of these whole-genome sequencing-based data, which are often more reproducible than phenotypic data,3 could also lead to a reconsideration of the need for a fourth drug as part of first-line therapy, often considered an insurance policy against undetected resistance.7 Because all molecular drug susceptibility predictions will be reported concurrently, and eventually for up to 15 drugs, the results of whole-genome sequencing will present an opportunity to design bespoke treatment regimens early on, helping to minimise further amplification in the most resistant cases.

From the point-of-view of tuberculosis control, whole-genome sequencing will report evolutionary relationships between isolates with unprecedented granularity. Building on population studies that have been done in the past, routine roll-out will help to give the most precise nationwide insights to date into the number of cases transmitted locally and their transmission dynamics.8,9 This development is expected to inform control measures at local levels and policies at a national level.

The downstream effects of these advances on international health are keenly anticipated. If sequencing platforms progress as promised,5 portable (so-called lab-in-a-bag) technologies could help deliver these same benefits to where the need is greatest—to low-income, high-incidence settings, directly from clinical samples whilst the patient waits. Over and above the MTB/ RIF Xpert, whole-genome sequencing platforms could provide near to complete data to inform clinical decision making, indicating which drug to give, not just which to avoid. This month's launch therefore marks only the very beginning of a new era in mycobacteriology. Whether other organisms will follow suit remains unclear. *M tuberculosis* is, after all, the organism among all bacterial pathogens with the greatest need and the greatest potential to benefit from whole-genome sequencing-based diagnostics. *M tuberculosis* killed more people in 2015 than any other single pathogen, and yet delay to full microbiological diagnosis remains at weeks, and in many high-incidence, low-income settings is not achieved at all.10 A National Center for Biotechnology Information search shows that the number of publically available *M tuberculosis* sequences already exceeds 25 000, but much is still to be learnt. As the number of sequences from routine diagnostics accumulate, the pace of change will only accelerate. In this respect, at least, we live in exciting times.

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