Developing best practice public health standards for whole genome sequencing of *Mycobacterium tuberculosis*

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Mycobacterium tuberculosis is a priority pathogen for global control. A growing number of countries have begun to incorporate routine whole genome sequencing (WGS) to support key aspects of tuberculosis (TB) public health and clinical practice, including monitoring of laboratory and clinical practices, detection and surveillance of drug resistance, and guidance of targeted public health interventions such as expanded contact investigation and active case finding. However, enhanced structures, workforce capacity and monitoring systems are required to support effective translation of pathogen genomics into clinical and public health practice. We consider key elements for embedding WGS into routine TB service delivery.

A variety of WGS implementation models exist, with most services initially established with research grants or other short-term project funds. However, given the need to build a skilled multidisciplinary workforce and sustainable laboratory services, reliable long-term funding is essential. Multidisciplinary team members should include expertise in mycobacterial diagnostics, culture and genomics, advanced bioinformatics, and geospatial mapping, linking closely with clinical medicine and patient care, field epidemiology, public health and health policy. Programs also need guidance from social work, ethicists and context-specific cultural workers, and should actively engage TB affected communities when reviewing apparent clustering and planning precision public health responses.

The incorporation of WGS data into public health programs will introduce change at the micro (individual), meso (population) and macro (policy) levels[1] (Fig. 1). At a micro level, genomic data allows recognition of possible person-to-person transmission[2] and may identify instances of laboratory contamination, allowing unnecessary treatment to be discontinued.[3] Rapid genotypic identification of drug resistance informs personalised patient management, while WGS clustering identifies transmission and guides better targeted public health responses, particularly in low incidence settings where transmission is uncommon.[4]

Beyond individual treatment and transmission evaluation, WGS information should be combined with broader epidemiological data to evaluate emerging trends in drug resistance, perform higher level transmission tracking and assess geospatial 'hot spot' distribution. This meso-level analysis can inform program–level activities. For example, genomic data may identify underappreciated TB transmission in people from the same cultural background, geographic area or shared recreational activities not identified by standard epidemiological evaluation.[5] Such information may guide active case finding or use of preventive therapy, as well as the provision of culturally appropriate education and information to access tuberculosis services.

At the macro level, WGS data could shape TB program and health service policy and practice. Different epidemiological contexts may limit formulation of universal targets, but serial evaluation can provide useful metrics for service improvement. Adopting a standard

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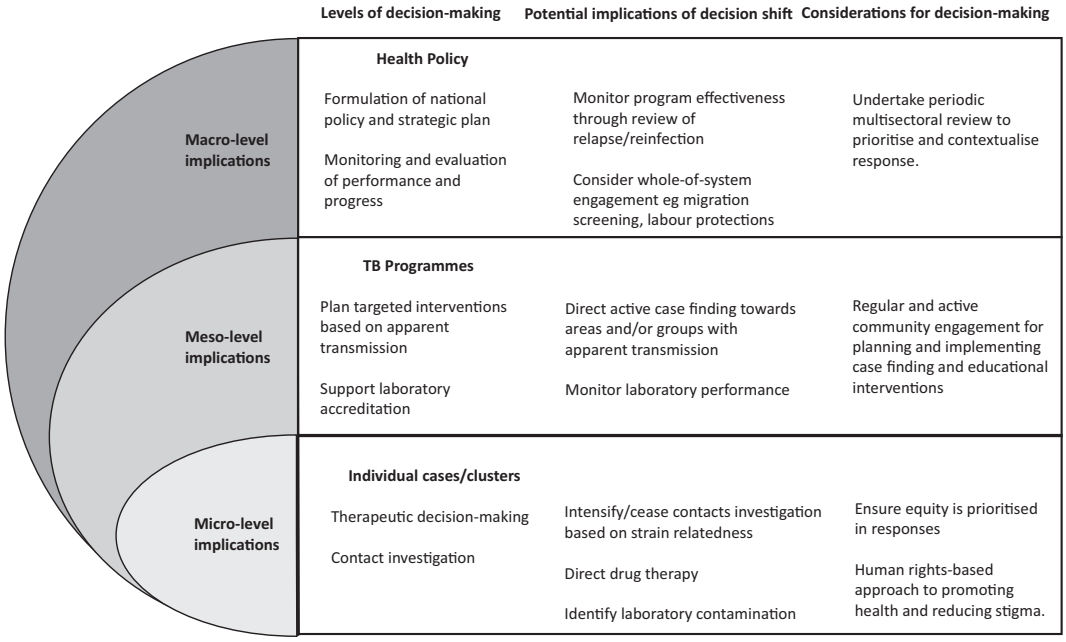

Fig. 1: Levels of decision-making and examples of public health application of M tuberculosis whole genome sequencing. Adapted from Sawatzky R, Kwon JY, Barclay R et al. Implications of response shift for micro-, meso-, and macro-level healthcare decision-making using results of patient-reported outcome measures. Quality of Life Research. 2021; 30:3343–3357.

approach to such analysis, such as monitoring the proportion of cases clustered using a 5-SNP threshold over a 5-year rolling average, will facilitate benchmarking between similar contexts and programmatic review of trends over time.[6] However, associating transmission clusters with potential discriminatory factors such as country of birth, geographical location or behavioral characteristics may result in harms to affected communities, which should be carefully considered.[7]

Public health genomics frequently lacks robust measures for evaluating impact.[8] While timely genomic sequencing may have clinical and public health benefit, better structured multimodal evaluation approaches would add value. This evaluation should include assessment of epidemiological impact of public health interventions as well as equity in key groups affected by TB, and health economic analysis, ideally incorporating public health and patient-level costs, rather than just laboratory costs. Assessing the importance and acceptability to patients and affected communities using co-design approaches is also important as are qualitative measures considering impact on policy and practice, such as use by clinicians and public health officials to inform treatment and isolation decisions based on WGS findings. Despite reducing costs, the financial and infrastructure requirements of WGS remain prohibitive for lower-resource settings, especially given current reliance on culture-based pathways for WGS. Concerted efforts are required to increase the access that lower-resource settings, which are often high TB incidence settings, have to the most relevant and locally useful WGS advances.[9] Ongoing development and routine use of WGS in high-resource settings should include active support for its global implementation, with an emphasis on equitable access to its individual and public health benefits.

There is great potential benefit from increased sharing of genomic data between jurisdictions and agencies. However, such exchanges are associated with ownership and privacy concerns,[10] and also require better standardization to facilitate data comparison and exchange. Establishing data sharing agreements and common pipelines is helpful but needs to ensure data security and must appropriately balance benefits and burdens. A robust legal framework is also essential, recognizing increasing requests to provide such data to assist with both public and private investigations.

In conclusion, the integration of routine WGS into TB control responses offer potential for significant benefit, but thoughtful application and evaluation is required to optimise public health value and to ensure that communities affected by TB stand to benefit from these advances.

Declaration of interests
All authors declare that they have no competing interests in this manuscript and its publication.

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