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Whole-Genome Sequencing To Guide the Selection of Treatment for Drug-Resistant Tuberculosis

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We welcome the work by Heyckendorf et al. (1) on the impact of phenotypic versus molecular testing on therapeutic selection for drug-resistant tuberculosis (DR-TB). The authors demonstrated the ability to accurately predict resistance and subsequently design an appropriate treatment regimen correlated with the proportion of the genome analyzed (1). In a comparison of phenotypic drug susceptibility testing (pDST), the average agreement in regimen selection was 93% with whole-genome sequencing (WGS), which decreased drastically to 49% and 63% when the Cepheid GeneXpert MTB/RIF and line probe assays, respectively, were compared. These findings highlight the role of WGS in providing a comprehensive molecularly based susceptibility profile to effectively guide clinical management of DR-TB. Heyckendorf et al. further underscore the underestimation of pDST to identify true resistance due largely to inappropriate critical concentration values. This has grave implications for tuberculosis control programs, evidenced by the current rates of TB drug resistance rates. Furthermore, the results of their study raise considerable concern regarding the lack of ethambutol (EMB) and pyrazinamide (PZA) resistance detection by current molecularly based testing algorithms (1). Given the role of these agents as companion drugs in both the intensive and the continuation phase of the current short-course MDR-TB regimen (2), we highlight the possible negative impact of undetected resistance on treatment response. Published reports on population-based surveillance data among patients with MDR-TB indicate that resistance to EMB and PZA ranged between 59.7 and 94.4% and between 59.3 and 81.8%, respectively, in patients with DR-TB (3). PZA is considered a desirable agent for the treatment of DR-TB due to its significant sterilizing activity and enhanced penetration into lung tissue (4). However, the selection of PZA resistance during first-line therapy and its subsequent impact on the development of pre-extremely drug-resistant TB under PZA-containing treatment has been demonstrated (5). Thus, we strongly advocate testing of susceptibility to all recommended drugs in standardized regimens to inform optimal drug selection. Screening for resistance has been associated with considerable challenges with regard to both phenotypic and genotypic testing platforms and the subsequent interpretation of resistance for clinical translation. Advances in sequencing technology have made great strides in understanding drug resistance. Furthermore, initiatives such as data-sharing platforms and international consortiums aimed at analyzing large-scale WGS data are close to addressing discordance between the various drug resistance testing platforms in order to accurately inform drug selection (Relational Sequencing TB Data Platform [ReSeqTB], https://platform.reseqtb.org/; Comprehensive Resistance Prediction for Tuberculosis: an International Consortium [CRyPTIC], http://www.crypticproject.org/). Where drug susceptibility is not

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known, toxicities associated with inclusion of drugs in a treatment regimen should be taken into consideration when making therapeutic decisions. One option worthy of consideration in the absence of a drug susceptibility profile is the exclusion of drugs known to have high background resistance to decrease adverse reactions and reduce pill burden. These data also emphasize the need for comprehensive susceptibility testing to maximize the role of new, shorter treatment regimens and new anti-TB drugs, such as bedaquiline and delamanid, and underscore the role of enhanced case management by DR-TB clinicians to ensure optimal treatment outcomes.

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