We thank Dr. Navisha Dookie and colleagues for their comments and for sharing their view on genotypic drug susceptibility testing (DST) to predict phenotypic drug susceptibility for the management of patients with drug-resistant tuberculosis (1, 2). We agree that DST should ideally be conducted for all drugs in a regimen, particularly given the severe adverse effects of second-line antituberculosis drugs. Yet, even whole-genome sequencing is not a one-size-fits-all solution. Instead, the goal has to be to optimally combine genotypic and phenotypic assays in a diagnostic algorithm that capitalizes on the strengths of both approaches while including appropriate reflex and confirmatory testing to minimize the impact of their respective limitations, including systematic errors (3).

In this context, a first important step was that our data were pooled with MIC and genotypic DST results from numerous additional studies to form the basis of a comprehensive systematic review of the breakpoints for 11 second-line drugs and for the new antituberculosis drugs bedaquiline and delamanid by the World Health Organization (WHO) (4). Based on the findings of this review, which two of us led in collaboration with Sophia Georghiou from the Foundation of Innovative New Diagnostics (FIND), and extensive deliberations by a Technical Expert Consultation Group, the WHO revised or newly established 20 breakpoints, which are now being adopted globally for routine phenotypic DST (4). Importantly, five breakpoints for fluoroquinolones or second-line injectables (i.e., levofloxacin, moxifloxacin, kanamycin, and amikacin), which represent the backbone of the regimens for drug-resistant tuberculosis, were lowered (i.e., for years, some strains that were likely resistant to these drugs have been systematically misclassified as susceptible by the old breakpoints [4]). These revised breakpoints will also reduce the frequency of discordant results between genotypic and phenotypic DST.

We are currently working on aligning the interpretation of the Hain GenoType MTBDRsl (v2) with the new breakpoints and on developing a set of “expert rules” to
define in which situations particular resistance mutations should be considered the gold standard for ruling in resistance (i.e., to recommend not to conduct phenotypic DST in these specific cases, as this may risk misclassifying them as susceptible, and for the genotype to overrule any susceptible phenotypic results). Such nuanced approaches are essential to facilitate more-personalized treatment of patients with multidrug and extensively drug-resistant tuberculosis in the future.

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