To the Editor—We studied with great interest the novel treatment guidelines for drug-susceptible tuberculosis [1]. The authors mention situations where therapeutic drug monitoring (TDM) may be useful: drug malabsorption, drug underdosing, and drug–drug interactions. Limited availability in low-resource settings, sample stability, and costs meant that TDM was not advocated for drug-susceptible tuberculosis [2] but endorsed
for multidrug-resistant tuberculosis [3]. Nahid and colleagues emphasize that no prospective randomized controlled trials (RCTs) are available to define the role of TDM in tuberculosis treatment [1].

Indeed, an RCT may define in which subpopulations TDM has the most impact and allow quantification of that impact to support additional cost analyses. Yet, the pharmaceutical industry would generally decline support of a trial without a new drug regimen, and public funding remains competitive and focused on regimens that may shorten total treatment duration. Short of a new trial, do we not already have sufficient evidence that shows that drug exposure to, for example, isoniazid is relevant for outcome [4]? Early bactericidal activity studies show a clear association between dose (ie, exposure) and reduction in bacterial load [5]. An RCT demonstrated that dose selection based on N-acetylation polymorphism resulted in less treatment failure in rapid acetylators and fewer adverse drug events in poor acetylators [6]. Although not tested, this makes a strong case for TDM. The guidelines mention that low drug exposure did not translate into poor outcome in some studies. Yet in these studies, TDM was used only after patients have manifested slow response to therapy where equivalence in outcome could instead be interpreted as an actual benefit conferred by TDM in preventing the more rare events of relapse or acquired drug resistance. Moreover, optimal assessment of drug exposure should always be related to a patient’s actual Mycobacterium tuberculosis minimum inhibitory concentration (MIC), and the time that TDM focuses only on drug exposure has passed [7]. Commercially available MIC plates are accurate and operationally acceptable [8]. But could we expect widespread implementation of TDM by 2 serum samples collected at 2 and 6 hours after drug intake and sent frozen to a certified laboratory? Likely not, as such a shipment is often not feasible. However, dried blood spot analysis (DBSA) is a game-changing alternative [9]. Sample collection is now easier using a drop of blood from a finger-prick collected on a card, which can be shipped at ambient temperature by mail.

Indeed, we agree with authors that the benefit of TDM may be higher in patients with malabsorption, human immunodeficiency virus coinfection, diabetes, or delayed spumtum culture conversion. However, we favor operational studies using DBSA to assess the application of early TDM in those subpopulations. TDM should be considered a useful tool in supporting clinical decision making. DBSA renders TDM feasible in many situations [10]. We expect such work will ultimately change the perception that TDM is only for specialized centers in low-prevalence settings, and instead considered as an important tool in the global fight against tuberculosis.

Note

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