More seriously, in randomized trials, reinfection events should be randomly distributed between the treatment arms and carry no information about the efficacy of treatment. The strong determination of “recurrence” by host factors that the authors seem to be proposing would only appear to support this traditional view. By contrast, true “relapses” are believed to be causally related to the efficacy of therapy, yet it would appear that few such patients were included in the study of Mistry et al. Thus, expression patterns of host genes persisting after clinical cure could reasonably be expected to predict reinfection events in a matched design with a high proportion of the data set devoted to training. This result, however, gives little assurance that the same discriminant function could be successfully applied directly to new data sets with greater interindividual variability in expression and a lower proportion of reinfections. It is even possible that different functions or sets of genes would be selected for different study populations, raising the question of how these composite biomarkers should be compared.

In general, for a biomarker to be used as a surrogate end point for the evaluation of new treatments in a clinical trial, differences in the biomarker should reliably predict the difference in clinical outcome between 2 treatment groups (trial level surrogacy) [4]. Showing even perfect association between a biomarker and the clinical end point (individual level surrogacy) is neither sufficient nor necessary to qualify the biomarker as a useful trial level surrogate [5]. To draw an analogy with a related field, it is well known that CD4 cell count is a useful individual-level surrogate for disease progression in HIV-infected individuals, but several studies have shown that change in CD4 cell count during antiretroviral therapy is a poor trial-level surrogate [6–8].

The authors describe an approach that may be capable of discriminating between patients who are cured and those who will later relapse, and this could ultimately be useful in clinical practice. To “facilitate clinical trials of new chemotherapeutic agents or shortened treatment” [1, p. 363] however, it must also be demonstrated that the biomarker fully captures the effect of treatment on the clinical end point. It is encouraging that new biomarkers are in development that could ultimately improve on intermediate bacteriological results in tuberculosis trials, but we believe that more consideration needs to be given to the methods by which these new tools are to be evaluated.

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clinically valuable for prediction of TB treatment outcome on an individual basis, which will be necessary to detect improvement over the current treatment protocol with its recurrence rate of around 5%.

We believe the inclusion of host factors could increase sensitivity over microbiological testing alone, particularly as the majority of patients with TB are sputum culture negative after 3 months but may still experience TB recurrence. The host immune system is intricately linked with TB disease pathogenesis, and changes in the immune response can be observed during treatment [2–4]. Immunosuppression that is present at diagnosis in patients with TB is reduced by therapy, with a concomitant reduction in the proportion of regulatory T cells [5]. We have already identified host biomarkers that associate with treatment response [6], and our transcriptomis study was performed to identify new candidate biomarkers.

The issue concerning the time point of testing in the recurrent group is one that we have been considering for a long time. The majority of HIV-negative people who are infected with *Mycobacterium tuberculosis* never succumb to disease, and the majority of treatment-adherent patients with active TB do not have TB recurrence. We therefore believe that this recurrent group represents people who are highly susceptible to TB disease and therefore were a good target group to identify our biomarkers. People who have TB relapse after conventional treatment after infection with drug-sensitive organisms are likely to be such highly susceptible individuals.

We believe the strength of our study is the demonstration that groups of patients with TB can be classified using host gene expression in blood.

To test the predictive value of biomarkers in a prospective study, large numbers of patients must be recruited because of the expected 5% TB recurrence rate. This is logistically challenging, but we have now collected samples from such patients and will test the correlation of expression of our biomarkers with treatment outcome.

Optimal time points during treatment can also be identified. Such samples may also be used for the identification of further biomarkers using microarray technology, now that we have established proof-of-principle. We hope that the publication of the data from our cross-sectional pilot study will allow other investigators to test them in different geographical locations and situations.

An issue that Davies et al. do not address is the one of matching. This shows the complexity of the topic. Does one match for clinical characteristics known to be associated with recurrence, such as cavitation on chest x-ray? Or are such characteristics dependant on whatever underlying cause there may be for recurrence, and by matching one thereby introduces a bias that will obscure the relevant markers?

Ultimately, we expect an algorithm to be developed that will combine host and microbiological biomarkers, together with clinical factors such as extent of disease at diagnosis, to reliably predict TB recurrence after treatment. Such an algorithm would then need to be rigorously tested in a clinical trial setting as described by Davies et al., to determine whether it is useful as a surrogate marker of cure.

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Randomized, Controlled Trial of Treatments for Second-Stage Sleeping Sickness

To the Editor—The trial reported by Bisser et al. [1] is a carefully conducted study undertaken in the challenging field of human African trypanosomiasis (HAT) and adds data that may influence future studies and policies. These data are amenable to alternative methods of analysis for several reasons.

The trial’s stated aim was to assess equivalence between 3 alternative treatment regimens and standard melarsoprol therapy, using relapse as an effectiveness criterion and an equivalence margin of 15%. It is apparent that any improvement in efficacy would be welcomed, particularly given that all of the alternative regimens are easier to administer than standard melarsoprol. Therefore, the 15% margin should not be applied symmetrically but only on the inferiority side, rendering noninferiority a more appropriate approach than equivalence. In fact, the statistical analyses undertaken by Bisser et al.