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From the authors:

We thank O. Moran Mendoza for his comment on the joint systematic review and meta-analysis on the role of interferon- γ release assays (IGRAs) for the diagnosis of latent infection with *Mycobacterium tuberculosis* by the Tuberculosis Network European Trials Group (TBNET) and the European Centre for Disease Prevention and Control (ECDC) [1]. O. Moran Mendoza highlights the as-yet limited knowledge about the positive predictive values of IGRAs for the development of tuberculosis, a standpoint that is also expressed in the new European Union guidance on the use of IGRAs in support of the diagnosis of tuberculosis [2].

In our meta-analysis and systematic review, only studies reporting on the diagnosis of latent infection with *M. tuberculosis* (LTBI) that used the latest commercially available version of IGRAs were included. Studies that were performed with “in-house” IGRAs, *e.g.* the studies by HILL *et al.* [3] and by BAKIR *et al.* [4], were not considered. Although it was not the focus of our review, differences between the studies with commercially available IGRAs and these two studies should be highlighted. Among the 26 contacts who developed active tuberculosis in the study by HILL *et al.* [3] from Gambia, no clear linkage of secondary tuberculosis cases to the putative index cases could be established. In addition, the authors used a slightly different cut-off for IGRA positivity, limiting direct comparison of the results. BAKIR *et al.* [4] performed a primarily interventional study. Most of the household children and adolescent contacts with a positive tuberculin skin test (TST) or IGRA result received isoniazid preventive chemotherapy for a duration of 6 months. This intervention was ~60% effective at preventing tuberculosis and, thus, substantially influenced the evaluation of the prognostic value of IGRAs for the development of tuberculosis.

In the European region, two large studies that have addressed the positive predictive value of latest-generation IGRAs for the development of tuberculosis have been published to date. While DIEI *et al.* [5] found a clear superiority of an IGRA over the TST for the development of tuberculosis in household contacts, KIK *et al.* [6] found IGRAs and the TST equally ineffective at predicting the development of tuberculosis in immigrants to the Netherlands. As the study populations investigated were different and KIK *et al.* [6] performed IGRAs only when the TST was positive, the results of both studies are not directly comparable.

In countries of low-to-medium tuberculosis prevalence, short-term progression rates to tuberculosis in individuals belonging

to tuberculosis risk groups have been reported to range from 3.3% to 12.9% [5–9]. Although the potential cost-effectiveness of an IGRA for the investigation of LTBI has recently been demonstrated in immigrant screening in the UK [10], information on the predictive values of IGRAs for the development of tuberculosis still relies on a small number of at-risk individuals who actually developed tuberculosis. Clearly, more information is needed before general recommendations that IGRAs should replace the TST can be made.

Future prospective studies that will address the role of immunodiagnosis in tuberculosis risk assessment should focus on stratification of subjects into different risk groups and be performed in multiple centres.

There is a striking difference in the positive and negative predictive values of the TST and IGRAs for the diagnosis of tuberculosis. While the negative predictive values for all tests in clinical use are >97%, the positive predictive values are low and the large majority of individuals at risk for the development of tuberculosis with a positive TST and/or IGRA result will not develop tuberculosis. Clinical decision makers in many countries are, therefore, hesitant to advocate consequently for preventive chemotherapy despite positive test results. Biomarkers for the prediction of tuberculosis need to be substantially improved beyond the limited performance of the TST and IGRAs, and treatment duration should be shortened substantially. Advocacy of preventive chemotherapy by caregivers and acceptance by individuals at risk for the development of tuberculosis need to be improved. As a general rule, testing should only be offered to those individuals belonging to at-risk groups to identify those with the highest risk for future tuberculosis development.

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Increase in walk distance is not enough evidence to add a walk to the 6-minute walk test

To the Editors:

We read with interest the work of HERNANDES *et al.* [1]. The authors performed a cross-sectional analysis using data from 1,514 patients with moderate-to-very severe chronic obstructive pulmonary disease who performed 6-min walks on consecutive days and recommended that, because the distance of the second walk was longer than that of the first, two walks should be performed [1]. Their finding that the walk distance increases by 7% on the second walk (27-m increase from a baseline of 391 m) validates our previous findings and adds new knowledge about the variables that predict improvement in walk distance [2]. These predictors of improvement may be helpful in identifying which subgroups of patients may benefit the most from performing two walks instead of one per 6-min walk test.

However, documenting an increase in walk distance is not enough evidence to add an additional walk to the 6-min walk test. To determine whether an additional walk should be performed, the authors should investigate whether adding a second walk makes the test more accurate, *i.e.* allows better correlation of changes in walk distance with a gold-standard measurement of exercise capacity, such as a cardiopulmonary exercise testing, or a better representation of change in patient-reported activity limitation measured by symptom-based questionnaires [3]. Also, it should be determined which walk distance leads to more precise test results over longitudinal follow-up, *i.e.* has less random error reflected by a smaller standard deviation. Less random error would lead to reduced sample size requirements for clinical trials that use improvement in walk distance as the end-point, which will make these studies much more feasible. If the second walk were to appear superior in these analyses, the magnitude of the benefit would have to be weighed against the added cost and effort required for a second walk. Unfortunately, the authors do not include a gold-standard measurement of exercise capacity,

patient-reported exercise limitation, longitudinal follow-up or data on relative magnitude of benefit, and therefore, do not provide enough evidence to support their recommendation to add a second walk.

Even if an additional walk were to be performed, should we be using the second walk distance as the formal result of the test in all our patients, as implied by the authors [1]? 18% of their patients walked a shorter distance on the second walk. This could have occurred for a number of reasons, such as residual fatigue from the first walk or a lack of motivation to repeat the walk distance. In such cases, this shorter second walk distance may not best represent true exercise capacity; rather, the best of two, or even an average of two, walk distances may be a better alternative. However, HERNANDES *et al.* [1] did not determine the optimal interpretation of the two walk distances.

To support their recommendation for using the second walk distance, the authors make indirect arguments in their discussion based on a Bland–Altman analysis that compared the first walk distance to the second. However, the Bland–Altman analysis is a test of agreement, and cannot be used to determine which measurement is better [4].

Therefore, noticing an increase in the 6-min walk distance and identifying factors that predict the increase is a useful addition to our understanding of the 6-min walk test, but does not provide enough evidence to recommend an additional walk be performed. Unless such evidence becomes available, the benefit of a second 6-min walk remains speculative [5].

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