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Statement of Interest: None declared.

REFERENCES

1 Solovic I, Sester M, Gomez-Reino JJ, *et al.* The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J* 2010; 36: 1185–1206.
2 Tsiouri G, Gaitanis G, Kiorpelidou D, *et al.* Tuberculin skin test overestimates tuberculosis hypersensitivity in adult patients with psoriasis. *Dermatology* 2009; 219: 119–125.
3 Bassukas ID, Kosmidou M, Gaitanis G, *et al*. Patients with psoriasis are more likely to be treated for latent tuberculosis infection prior to biologics than patients with inflammatory bowel disease. *Acta Derm Venereol* 2011; [Epub ahead of print DOI: 10.2340/00015555-1106].
4 Laffitte E, Janssens JP, Roux-Lombard P, *et al.* Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-γ release assay *versus* tuberculin skin test. *Br J Dermatol* 2009; 161: 797–800.
5 Goujon C, Gormand F, Gunera-Saad N, *et al.* Pertinence des critères diagnostiques de tuberculose latente avant traitment du psoriasis par anti-TNF-α. [The relevance of diagnostic criteria for latent tuberculosis before initiation of TNF-alpha inhibitors in psoriasis patients.] *Ann Dermatol Venereol* 2010; 137: 437–443.
6 Fuchs I, Avnon L, Freud T, *et al.* Repeated tuberculin skin testing following therapy with TNF-α inhibitors. *Clin Rheumatol* 2009; 28: 167–172.

DOI: 10.1183/09031936.00016611

From the authors:

We thank our colleagues for their comment on the TBNET consensus statement on the risk of tuberculosis (TB) related to tumour necrosis factor (TNF) antagonist therapies [1]. The authors correctly point to a persistent diagnostic dilemma: the diagnosis of ''true'' latent infection with *Mycobacterium tuberculosis* [2] and the lack of knowledge on the positive predictive value for the development of TB offered by the two currently available immunodiagnostic methods, the tuberculin skin test (TST) and interferon-γ release assays (IGRAs), in a variety of clinical circumstances [3].

By definition, the diagnosis of latent infection with *M. tuberculosis* relies on the presence of a positive *M. tuberculosis*-specific immune response in a TST or an IGRA. However, the immunological diagnosis of latent infection with *M. tuberculosis* is a relatively poor approximation of ''true'' latency [2]. The concept of preventive chemotherapy relies upon the identification of individuals who are at highest increased risk for the development of TB by positive *M. tuberculosis*-specific immune responses. Screening and treatment for latent infection with *M. tuberculosis* is only effective, efficacious and efficient when populations with a *per se* increased risk for the future development of TB are targeted [4]. These include recent close contacts of contagious index cases, individuals with HIV infection, subjects with silicosis, candidates for TNF antagonist therapies, patients with chronic renal failure, individuals with immunosuppressed stem cell, solid organ recipients, and others [5].

While the risk for the development of TB is strikingly different among patients, depending on the absence or presence of a specific risk factor [6], percentages of positive *M. tuberculosis*-specific immune responses are also heterogeneous when comparing groups of patients at increased risk for the development of TB. At the group level, population epidemiology matters. For example, in Europe, positive TST and/or IGRA responses have been observed in only 10–15% of individuals with HIV infection, compared with ~25% of patients with chronic renal failure [7]. But the risk for the development of TB is higher among individuals with HIV infection than in patients with chronic renal failure [5]. What we are able to observe is the combined effect of underlying prevalence of infection, which we try to estimate more or less successfully with a test and the risk of TB given actual latent infection. Although the underlying mechanism may be different, the reported high percentage of positive *M. tuberculosis*-specific immune responses in patients with psoriasis [8] might not be indicative that psoriasis patients with a positive TST and/or IGRA response benefit as much from preventive chemotherapy against TB as other candidates for TNF antagonist therapies.

We agree with our colleagues that the percentage of positive *M. tuberculosis*-specific immune responses is likely to vary between different groups of patients with candidates for TNF antagonist therapies. The probability of a positive TST or IGRA is, among other factors, certainly related to the underlying clinical condition. As the predictive value of a positive test hinges largely on the prevalence and individual future morbidity risk, as well as on the absence or presence of defined risk factors and their magnitude if present, it would therefore be critical to obtain more precise information separately for each group of individuals at potentially increased risk of TB. However, until we have such evidence, we should be cautious and state, using the lowest possible evidence grading of ''D'', that screening for latent *M. tuberculosis* infection and preventive chemotherapy against TB should not be different for distinctive groups of patients with underlying diseases (rheumatoid arthritis, psoriasis, inflammatory bowl disease) who are candidates for TNF antagonist therapies.

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Statement of Interest: None declared.

REFERENCES

1 Solovic I, Sester M, Gomez-Reino JJ, *et al.* The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J* 2010; 36: 1185–1206.
2 Mack U, Migliori GB, Sester M, *et al.* LTBI: latent tuberculosis infection or lasting immune responses to *M. tuberculosis*? A TBNET consensus statement. *Eur Respir J* 2009; 33: 956–973.
3 Diel R, Goletti D, Ferrara G, *et al.* Interferon-γ release assays for the diagnosis of latent *Mycobacterium tuberculosis* infection: a systematic review and meta-analysis. *Eur Respir J* 2011; 37: 88–99.
4 Lange C, Rieder HL. Intention to test is intention to treat. *Am J Respir Crit Care Med* 2011; 183: 3–4.
5 Leung CC, Rieder HL, Lange C, *et al.* Treatment of latent infection with *Mycobacterium tuberculosis*: update 2010. *Eur Respir J* 2011; 37: 690–711.
6 Erkens CG, Kamphorst M, Abubakar I, *et al.* Tuberculosis contact investigation in low prevalence countries: a European consensus. *Eur Respir J* 2010; 36: 925–949.
7 Sester M, van Leth F, Girardi E, *et al.* Head-to-head analysis of IGRAs and skin-testing in immunocompromised patients: interim analysis of a multicenter TBNET study. *Eur Respir J* 2010; 36: Suppl. 54, 370s–371s.
8 Tsiouri G, Gaitanis G, Kiorpelidou D, *et al.* Tuberculin skin test overestimates tuberculosis hypersensitivity in adult patients with psoriasis. *Dermatology* 2009; 219: 119–125.

DOI: 10.1183/09031936.00041811

Internal consistency of reference equations

To the Editors:

In a recent *European Respiratory Journal* paper addressing the choice of reference values for spirometric indices, mean z-scores were used to quantify deviation from a large collated data set or to establish the absence of secular trends in forced expiratory volume in 1 s (FEV_1) or forced vital capacity (FVC) [1]. Yet, once an appropriate set of reference equations is selected for use in any given laboratory, it is equally important to assess whether these equations are internally consistent, *e.g.* in terms of age dependency of the various parameters under study. When consulting the most recent standardisation documents for guidance on the choice of reference equations [2, 3] the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force literally states ''currently this committee does not recommend any specific set of equations for use in Europe''. Due to our laboratory's particular geographical location, we have thus far felt compelled to apply the European Community for Steel and Coal (ECSC) equations for adult spirometry and lung volumes. Through the various updates up to the 2005 ATS/ERS recommendation [2], many reference equations date back to the original 1983 document [4], which was compiled from all the available adult data at the time. Applying these equations, we are now faced with two cases of internal inconsistency.

While the age- and height-dependent prediction equations for FEV_1 and FVC separately lead to a predicted FEV_1/FVC value which is similar to the one computed directly from the FEV_1/FVC prediction equation in male subjects, this does not hold true for females. For a 175 cm tall male ranging 25–65 yrs, the difference between the predicted FEV_1/FVC value and the ratio of predicted FEV_1 and predicted FVC values ranges 2.0–2.5%. In a 165 cm female aged 65 yrs, the difference amounts to as much as 7.2%; indeed, the ratio of predicted FEV_1 and predicted FVC is 84%, as opposed to the predicted FEV_1/FVC value of 76.8%. Alternatively, the Third National Health and Nutrition Examination Survey (NHANES III) reference equations for Caucasians [5] lead to corresponding differences in FEV_1/FVC of $\leqslant$0.1%, for both sexes across the same age range. In comparison with the NHANES III prediction equations, both FEV_1 and FVC prediction equations are quite different, yet, the prediction equation for FEV_1/FVC is very similar to the ECSC one. This indicates that it is the relative age dependence of FEV_1 and FVC in females which is in error, due to an inaccuracy in either age dependence of FEV_1, in age dependence of FVC or in both. This inconsistency in the reference equations, or its derived limits of normal, is relevant for instance when determining prevalence of restriction (FVC) and obstruction (FEV_1/FVC) in the same population. Alternatively, when assessing both the presence of obstruction (FEV_1/FVC) and its severity (FEV_1), or quantifying lung age, based on either predicted FEV_1 or predicted FEV_1/FVC, an inconsistency between FEV_1/FVC and its components is likely to bias the outcome.

Another apparent discrepancy shows up in the ECSC reference equations of functional residual capacity (FRC), showing a very poor dependency on age in adult females and a nine-fold greater age-dependence in adult males. This is in contrast to a similar age dependence for boys and girls through to adulthood [3], and also in contrast to the reference equation of the largest of the data set on which the composite FRC reference equation is based, namely the 1,841 subjects investigated by W.J. Ulmer and co-workers as referenced by QUANJER [4]. These authors showed a similar age dependence for both sexes: a coefficient that is the same as in the ECSC equations for FRC in males, and an age coefficient in females being 78% of the coefficient in males. Obviously, the virtual absence of age dependence in predicted FRC for females in the ECSC reference equation may unduly identify an older female subject as hyperinflated. This may be particularly relevant to diseases and treatments involving hyperinflation, which make use of FRC or inspired capacity as an indicator.

We suspect that both these observations are merely the result of understandable limitations of ~30-yr-old reference equations, that are composite equations based on even older reference equations, and not on collated data sets of individual data points as suggested now [1]. This should encourage any current or future initiative to pool as many reliable data as possible before extracting reference equations, thereby avoiding