Interferon-γ release assays for prediction of tuberculosis

Molebogeng Rangaka and colleagues[1] have comprehensively reviewed the prognostic characteristics of interferon-γ release assays (IGRAs). Their findings show that the advantages of these assays are not offset by any loss of ability to predict development of tuberculosis in people with latent *Mycobacterium tuberculosis* infection.

Studies that directly compared the assay with the tuberculin skin test confirm the low accuracy of both for estimation of prognosis; tuberculosis will never develop in most people with a positive result from either test, but tuberculosis will develop in some who had negative results. Although the accuracy of both tests is disappointing, IGRAs are no worse—and for some comparisons are better—than tuberculin skin test.

In USA, the benefits of IGRAs support their wide adoption. First, most of our tuberculosis caseload has shifted to BCG-vaccinated immigrant groups, and IGRAs have greater specificity in this group.[2] Our experience in San Francisco, CA—where IGRAs have replaced tuberculin skin test in most settings—is that the proportion of immigrants and homeless people with positive test results decreased substantially after switching the in tests (table). The subsequent decrease in medical assessment improves efficiency and cost-effectiveness and fewer patients are inconvenienced by treatment and its toxic effects than if tuberculin skin test was used. The studies reviewed by Rangaka and colleagues report that IGRAs offer these benefits with fewer false-negative results than tuberculin skin test.

Second, up to 98% of IGRAs yield a usable result in San Francisco.[3] Yet, up to a third of our patients who receive a skin test do not return for the result (unpublished), and even lower return rates have been reported.[4] With IGRAs, community health workers can focus on people with positive results instead of searching for those without a result.

Third, locations such as ours include multiple health-care settings with different types of patient records. Most tuberculin skin test results are recorded only in individual patients' records, not in electronic databases. Results of IGRAs can be stored in laboratory databases for easy analysis.

We agree with Rangaka that a novel test that accurately predicts tuberculosis after *M tuberculosis* infection, or improved application of current tests, is essential for prevention. However, while we await the next breakthrough, the practical advantages of IGRAs are such that public health officials who focus on prevention of tuberculosis should consider adoption of these tests.

	TST*	IGRA†
Clinic for immigrants	1050/2825 (37%)	750/3391 (22%)
Clinic for homeless people	1726/6231 (28%)	506/7548 (7%)

TST=tuberculin skin test. IGRA=interferon-γ release assay. *January 2001–December 2003. †January 2008–May 2011.

Table: **Positive results for tuberculosis tests in San Francisco, CA, USA**

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New research and development strategy for tuberculosis diagnostics urgently needed

Mark Nicol and colleagues[1] provide the first assessment of Xpert MTB/RIF for diagnosis of paediatric pulmonary tuberculosis; they report high specificity for the test. Xpert MTB/RIF had a higher detection rate than did smear microscopy; however, sensitivity for paediatric samples was lower than for adults. Furthermore, the test was less sensitive than was culture for diagnosis of childhood tuberculosis,[1,2] although it provided results faster (1 day *vs* 12 days). Although Xpert MTB/RIF is a major advance for diagnosis of tuberculosis the results of this study show that some diagnostic challenges and limitations remain.

Mainly, the study shows the urgent need for improvements in methods to obtain and process respiratory samples. Nicol and colleagues did their study in settings where sputum induction could be done to produce good quality samples for diagnosis, and note that data for the use of sputum induction in primary-care facilities are scarce. In settings with many HIV-positive patients and children, inadequacy of samples is a limitation for Xpert MTB/RIF roll-out, because such patients are often unable to produce sputum specimens that are suitable for analysis, or the specimens obtained have a low bacterial load.[3] Techniques such as sputum induction can help but cannot be implemented

widely because they need equipment, infection control measures, and trained health staff. To improve diagnosis of tuberculosis in children and people with HIV/AIDS, a long-term goal should be to incentivise the research and development community to devise new diagnostics that are not based on sputum and prioritise the discovery of biomarkers (ideally based on pathogens) in samples other than sputum. Open access repositories for paediatric sample should be established to support this effort.

Roughly 60% of patients with tuberculosis worldwide present in peripheral health centres in resource-poor settings[4] where diagnostic tests based on sophisticated instruments such as Xpert MTB/RIF will not be feasible. These centres might not have electricity or running water, and have few or no laboratory facilities. Therefore, an urgent challenge remains to ensure that new diagnostic tests are suitable for use in peripheral health facilities in resource-poor countries. The research and development community must focus on delivery of a point-of-care diagnostic test for tuberculosis, as for HIV diagnostics, for which patients can be diagnosed and offered treatment within hours of testing.

Our view is that research and development for tuberculosis diagnostic tests could be vastly improved by adoption of a more strategic and collaborative approach focused on a point-of-care test; a new strategy is needed to ensure quicker progress. Our assessment of current research and development[5] identified an urgent need for improved integrated planning between areas of biological discovery, increased test development and specimen repositories, and increased funding from donors and improved collaboration between researchers. Such changes could deliver a point-of-care tuberculosis test within 5–7 years that would revolutionise diagnosis and treatment of tuberculosis worldwide.

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HIV-1 drug resistance in antiretroviral-naive patients in sub-Saharan Africa

We read with interest the Article[1] by Ralph Hamers and colleagues, and their conclusion that high drug resistance in Uganda resulted from early roll-out of antiretroviral therapy. Our alternative interpretation is that both the duration of access to treatment and the effect of poor treatment outcomes (ie, adherence and viral suppression) played a part.

In early 2005, as part of an infectious diseases team working in east Africa, we spent several months in Fort Portal, Uganda, setting up the second antiretroviral therapy programme in the city. Fort Portal is a rural town 300 km from Kampala with about 50 000 inhabitants and a generalised, heterosexual HIV epidemic. In 2004, the clinics in Uganda were crowded with large numbers of HIV patients with severe and advanced disease and the only systematic access to treatment in the Fort Portal region was one overwhelmed public facility. This facility had no resources other than antiretroviral drugs to care for these patients, and outcome measures focused on enrolment numbers not on adherence rates, retention in care, or viral suppression. Furthermore, scale-up in Uganda was rapid compared with other countries covered by the President's Emergency Plan For AIDS Relief, resulting in the country meeting its targets for antiretroviral therapy enrolment in the first 2 years of the programme.[2]

At the time, guidelines supported use of combination nevirapine, stavudine, and lamivudine for only late-stage patients. The absence of systematic community adherence programmes, coupled with little in-depth medical assessment, resulted in initial viral suppression rates of sometimes as low as 40–60%.[3] These shortcomings probably led to early development of resistance in thousands of treated patients and the subsequent spread of resistance to the surrounding community. Access to antiretroviral treatment in Uganda before the creation of the President's Emergency Plan For AIDS Relief and the Global Fund[4] was very low and this period was characterised by frequent treatment interruptions in Uganda and elsewhere in Africa.[5] Unfortunately, in many settings this poor access continues, and these interruptions drive the development of viral resistance. Development of community-wide resistance, as in Uganda, is mainly related to initial viral suppression achieved by the major treatment clinics for those communities and the resultant spread of resistant viruses, and not merely a