1 Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet* 2011; **377:** 1495–505.

2 Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010; **363:** 1005–15.

3 Kranzer K. Improving tuberculosis diagnostics and treatment. *Lancet* 2011; **377:** 1467–68.

4 Mwaba P, McNerney R, Grobusch MP. Achieving STOP TB Partnership goals: perspectives on development of new diagnostics, drugs and vaccines for tuberculosis. *Trop Med Int Health* 2011; published online April 13. DOI:10.1111/j.1365-3156.2011.02777.

Katharina Kranzer's Comment[1] accompanying the paper by Catharina Boehme and colleagues[2] highlights important limitations of the Xpert MTB/RIF assay, such as its shortfalls as an ideal point-of-care test and its use for detection of drug-resistant tuberculosis.

However, a shift of focus is now urgently required; the accuracy of the assay has been addressed.[2,3] We need to move on and assess its cost-effectiveness and how it will change the performance of national tuberculosis programmes in terms of detection rates and management of resistant forms of *Mycobacterium tuberculosis*. Although self-evident for any new test, it might be prudent to recall that an operational assessment should be done independently of the funders, developers, and manufacturers of the assay. Independent high-quality operational research in different geographical and economic settings is also required to show where, when, and how the new assay will provide clear advantages for health-care systems and patients.[4]

Although the Xpert MTB/RIF assay is recommended for screening of drug-resistant tuberculosis and for populations infected with HIV,[5] its high sensitivity in smear-negative cases could support other uses, such as for biomarkers of tuberculosis disease activity or cure.

Creativity and innovative solutions are needed to fill structural gaps in low-resource settings, and to ensure that this and similar new technologies can be appropriately and effectively implemented. Use of the Xpert assay will probably increase costs for national programmes; commitment by national governments and donors to consider this cost in their budgets is mandatory.

Introduction of the Xpert MTB/RIF assay marks the beginning of the revolution of tuberculosis diagnostics in the early part of the 21st century, but the hard part is still to come.

We declare that we have no conflicts of interest.

*Giovanni Ferrara, Justin O´Grady, Alimuddin Zumla, *Markus Maeurer*
markus.maeurer@ki.se

Centre for Allogeneic Stem Cell Transplantation, Karolinska University Hospital, Stockholm, Sweden (GF, MM); Section of Respiratory Diseases, Santa Maria Hospital, University of Perugia, Terni, Italy (GF); University College London Medical School, Division of Infection and Immunity, London, UK (JOG, AZ); and Department of Microbiology, Tumor and Cell Biology and Department of Laboratory Medicine, Karolinska Institutet, 17182 Stockholm, Sweden (MM)

1 Kranzer K. Improving tuberculosis diagnostics and treatment. *Lancet* 2011; **377:** 1467–68.

2 Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet* 2011; **377:** 1495–505.

3 Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010; **363:** 1005–15.

4 Sackett DL, Haynes RB. The architecture of diagnostic research. *BMJ* 2002; **324:** 539–41.

5 Stop TB Department, WHO. Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB. http://www.who.int/tb/laboratory/roadmap_xpert_mtb-rif.pdf (accessed April 25, 2011).

Authors' reply

In response to our paper on Xpert MTB/RIF,[1] Grant Theron and colleagues point out that a proportion of patients with tuberculosis, importantly some infected with HIV, will not be detected by Xpert testing. Clearly patients who expectorate very low concentrations of organisms could be misdiagnosed with all existing methods. In the case of microscopy and HIV-associated tuberculosis, this dilemma is acute. Xpert testing greatly diminishes, but does not eliminate, the likelihood that some tuberculosis will be missed. Since no test is 100% sensitive, health workers confronted with negative results from patients with suspected disease must: (1) retest a new sample, (2) test with alternative methods, or (3) treat on clinical bases. Xpert, despite sensitivity similar to solid culture, cannot resolve this dilemma.

Having said that, Theron and colleagues' calculation of negative predictive values from our study does not take into account the fact that these values are heavily dependent on local prevalence of disease. The demonstration study took place in six different countries with different prevalences of HIV infection and tuberculosis. The aggregate statistics published in our paper were balanced by stratification over these different study sites. Theron and colleagues base their conclusions on a tuberculosis prevalence of 35% in patients with HIV infection and 31% in patients without HIV infection (an average of each across sites). This particular combination was not identified in any single site and so the resulting aggregate is an oversimplification. The difference in sensitivity would, for example, not be significant if one applied 30% disease prevalence in both groups.

Fulvio Salvo and colleagues stress that the need for phenotypic drug susceptibility testing (DST) will not disappear with Xpert implementation. We agree, but note that, because DST availability is limited, Xpert provides an effective mechanism to focus resources on patients at high risk of drug resistance. Both phenotypic and genotypic testing result in some false calls: errors in DST for rifampicin occur with a frequency of 1–3% even in supranational laboratories.[2] In the quoted Dharamsala study, seven of 45 tuberculosis cases were rifampicin-susceptible on DST but resistant by Xpert by means of the then-available instrument software. This unusually high false-positive rate merits further investigation. Unfortunately *rpoB*

sequence information from these strains was not available. False-positive Xpert rifampicin resistance occurred during our demonstration projects, and triggered a root-cause analysis by the manufacturer, and a subsequent development plan to improve reagents, microfluidics, and software. Software solutions have been only partly successful, but we expect that the other refinements will eliminate most remaining false-resistance calls. Ideally, Xpert should equal or surpass DST reliability. In settings with a low prevalence of multidrug-resistant (MDR) tuberculosis, even low error rates would affect predictive values, and repeat molecular or phenotypic testing might be required. Countries will need to decide, depending on prevalence of MDR tuberculosis, second-line treatment availability, budget, phenotypic DST capacity, and how they handle Xpert results suggesting MDR tuberculosis.

Giovanni Ferrara and colleagues correctly point out that performance data provide an incomplete picture of a new diagnostic's usefulness. We also agree that implementing improved tuberculosis diagnostic testing will require substantial investment. Fortunately, Xpert MTB/RIF testing gets us very close to the goal of universal access to culture and DST without the need to construct unsustainable biosafety laboratories or wait for culture results.

MDP, PN, and CCB are employed by FIND, a non-profit organisation that collaborates with industry partners, including Cepheid, for the development, evaluation, and demonstration of new diagnostic tests. DA has served as a consultant to Cepheid and received royalties personally and to his laboratory under a licensing agreement between his institution and Cepheid. His royalties generated by the Xpert assay have been voluntarily, but irrevocably, capped at US$5000 per year (personal income) and $50 000 per year (laboratory income) to mitigate potential conflicts of interest. No commercial partner was involved in the study.

*Mark D Perkins, David Alland, Mark P Nicol, Pamela Nabeta, *Catharina C Boehme*
catharina.boehme@finddiagnostics.org

Foundation for Innovative New Diagnostics, 1202 Geneva, Switzerland (MDP, PN, CCB); New Jersey Medical School and Division of Infectious Diseases, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA (DA); and National Health Laboratory Service, Groote Schuur Hospital, Cape Town, South Africa (MPN)

1 Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet* 2011; **377:** 1495–505.
2 WHO. Anti-tuberculosis drug resistance in the world: fourth global report. http://www.who.int/tb/publications/2008/drs_report4_26feb08.pdf (accessed July 18, 2011).

Sharing information on adverse events

It is highly regrettable that you ran the letter by Koichiro Yuji and colleagues (May 14, p 1654)[1] which labels a report that ran in *Asahi Shimbun* as "misleading". The article from Oct 15, 2010,[2] was written from the viewpoint of protecting trial participants, and critically appraised a clinical trial at the Institute of Medical Science, University of Tokyo (IMSUT, to which one of the authors of the letter is affiliated) and other sites. Yuji and colleagues' letter contains serious misinterpretations of facts.

Our article reported that, despite a serious adverse event developing during the clinical trial of a cancer peptide vaccine at the IMSUT Hospital, IMSUT, as the vaccine developer, failed to report the incident to other clinical trial sites which had been supplied with the vaccine. The point of the article was to raise the question as to the appropriateness of the handling of safety information.

Yuji and colleagues wrote: "The newspaper seems to have interpreted a 'serious adverse event' as a 'significant complication' of the cancer vaccine." In fact, nothing in the article indicates confusion between an adverse event and a complication.

Yuji and colleagues also wrote: "In an Editorial, the newspaper went on to accuse the researchers of hiding the adverse event, and likened them to doctors in Nazi Germany." This sentence is also based on a misinterpretation. The *Asahi Shimbun* merely stated that the Declaration of Helsinki was developed as a response to human experiments carried out by the Nazis—it did not liken the clinical researchers to the Nazis.

I am the Editor in Chief of the Science and Medical News Section of the *Asahi Shimbun*.

Toru Omuta
kagaku@asahi.com

Science and Medical News Section, *Asahi Shimbun*, 5-3-2 Tukiji Chuo, Tokyo 1048011, Japan

1 Yuji K, Narimatsu H, Tanimoto T, Komatsu T, Kami M. Sharing information on adverse events. *Lancet* 2011; **377:** 1654.
2 Idegawa M, Noro M. The Institute of Medical Science, the University of Tokyo did not share the information of the adverse event to other research groups (in Japanese). *Asahi Shimbun* Oct 15, 2010.

Blood-cell banking for workers at the Fukushima Daiichi nuclear power plant


Asahi Shimbun via Getty Images

Tetsuya Tanimoto and colleagues (April 30, p 1489)[1] propose collection and storage of blood cells (equivalent to bone-marrow cells) from nuclear workers at the Fukushima nuclear power station, Japan, for possible use after accidental exposure to high-dose ionising radiation. We think that this recommendation is well intentioned but ill-advised for several reasons.

First, the best strategy in any nuclear or radiation exposure event is prevention. Workers at Fukushima are carefully monitored with dosimeters that detect external and internal radiation exposure levels. There are also numerous stable and robotic environmental monitoring devices.

Second, transplantation of blood or bone-marrow cells is relevant only if there is exposure to uniform, high-dose, whole-body radiation. Such exposure requires that the person be at a substantial distance from the radiation source (probably 3–4 m). Our study of the geometry of the Fukushima nuclear power station makes this type of exposure exceedingly unlikely.