the clinical laboratory, will act to build capacity at national and international levels, which is essential for the elimination of TB in low- and high-incidence settings.

In conclusion, genomics stands to significantly enhance TB elimination efforts through direct and indirect routes. When combined with the framework's recommended interventions, we believe WGS has the potential to accelerate progress towards TB elimination in low-incidence countries, with the knowledge gained in these settings working to support the final priority action area, thereby informing TB prevention, care, and control in countries with a high burden of disease.

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Genomics can aid TB elimination in low-incidence settings via enhanced epidemiology and rapid resistance prediction <http://ow.ly/TkPWS>

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From the authors:

We read with interest the correspondence by J.L. Guthrie and J.L. Gardy, which discussed the role of whole genome sequencing (WGS) in tuberculosis (TB) elimination based on the recently published World Health Organization (WHO) article [1]. The WHO document [1] focused on the priority interventions that should be applied by countries aiming to achieve TB pre-elimination (*i.e.* TB incidence <10 cases per million inhabitants) and elimination (*i.e.* TB incidence <1 case per million inhabitants) [1, 2]. The TB elimination strategy is expected to be initially adopted by low-TB incidence countries where the circulation of *Mycobacterium tuberculosis* strains is lower when compared to that observed in middle- and high-TB incidence countries.

On this basis, the WGS can represent an important clinical and public health tool, whose effectiveness was preliminarily demonstrated; although more operational research is needed to assess the feasibility and the potential impact of this technique. As pointed out by J.L. Guthrie and J.L. Gardy the WGS might play a crucial role in the identification of genomic strains' similarities and, then, in the true recognition of transmission dynamics in outbreaks. Tracking in-country and cross-border outbreaks by next generation sequencing can improve the identification of unsuspected transmissions allowing proper action to be taken.

The recently issued WHO guidelines on the programmatic management of latent TB infection (LTBI) raised the issue of the current diagnostic gaps for both LTBI and TB diseases, which could be filled by modern, rapid, and easy-to-use molecular- and biomarker-based techniques [3].

The European Centre for Disease Prevention and Control recommended a public health approach in the epidemiological investigations following the diagnosis of a TB case combining a conventional epidemiological approach with a molecular-based approach to better control outbreaks and ensure diagnosis and proper management of infectious cases [4]. In this context, the use of WGS as replacements for the current standard (i.e. mycobacterial interspersed repetitive units-variable number of tandem repeats) for molecular typing of strains is desirable when performed under appropriate, external-quality assurance programmes [5].

Furthermore, the possibility of rapid detection of genomic mutations associated with drug resistance could provide an important tool to better manage drug- and multidrug-resistant (MDR) TB. An immediate detection and notification to the local public health authorities will favour isolation of the contagious patient and the administration of targeted treatment, without any diagnostic and therapeutic delays, reducing the probability of further transmission while improving surveillance for drug resistance. Recent studies have described increasing proportions of new mutations in difficult-to-manage TB cases [6]; the possibility to rapidly “read” the entire mycobacterial chromosome allows a comprehensive genetic analysis to better manage the drug-resistant cases and their contacts. Large collaborative initiatives, such as the ReSeqTB (<http://www.cptrinitiative.org/programs/rapid-drug-susceptibility-testing/>), aimed at creating a centralised and quality global-TB relational sequencing data platform, which are needed to support the correct interpretation of molecular data for clinical management of patients and to guide the development of new molecular diagnostics designed for adoption world-wide [7].

Moving away from culture will only be possible when the sensitivity of current molecular-based diagnostics will be significantly improved and when protocols to perform WGS of *M. tuberculosis* directly from clinical specimens will be available and at an accessible cost. The process to implement WGS in high burden countries has already begun under the leadership of WHO and other international stakeholders. This process will guarantee equal opportunity to all in accessing the most up-to-date technology.

It is important to underline that the “hidden cost” of this technology is in the correct interpretation of the data for clinical purposes. At this stage we are still generating a large amount of data that we cannot properly interpret or translate into adequate treatment; improved understanding of the correlations between genetic mutations, drug susceptibility testing, and clinical outcome is, therefore needed.

This would be rapidly improved if scientists, clinicians, diagnostic companies and donors joined endeavours in generating high quality data that could be analysed in accordance with international standards in order to achieve sufficient confidence in the interpretation of each single genetic variant.

This process will require large collaborative efforts, bypassing the scientific competition in the interest of patients and their families, who unfortunately are still asked to pay a heavy economic tribute to TB in both low- and middle-income countries and, sometimes, in high-income countries (e.g. migrants) also [1, 8]. Within the spirit of the new WHO End TB Strategy and the perspective to achieve TB elimination the different stakeholders (including donors and scientific societies) need to collaborate in promoting the translational research activities necessary to improve diagnostic and treatment tools available for TB patients and their families [9].

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Whole genome sequencing may represent an important clinical and public health tool for tuberculosis elimination <http://ow.ly/TkGIIt>

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Linezolid in drug-resistant tuberculosis: haste makes waste

To the Editor:

HUGHES *et al.* [1] should be commended for their interesting short study on evaluating the efficacy of linezolid in drug-resistant tuberculosis (TB). However, there are some points of concern that need to be discussed. A recent systematic review and meta-analysis cautions the use of linezolid in multidrug-resistant (MDR) TB because of the frequency and severity of adverse events (*i.e.* peripheral and optic neuropathy, myelosuppression and gastrointestinal disorders), despite its excellent efficacy. This robust study recommends the use of linezolid in only severe and difficult-to-treat cases but under strict supervision [2].

The retrospective study included patients with MDR-TB, extensively drug-resistant (XDR) TB and pre-XDR-TB (this terminology, although not unanimously recognised everywhere, has been used by several clinicians and defined as MDR plus resistance to either a fluoroquinolone or an injectable agent) from resource constraint areas with high burden of TB. Under such a scenario it would have been prudent to start standardised treatment regimens as per the World Health Organization (WHO) guidelines [3], rather than individualised regimens without the feasibility of individual drug susceptibility test (DST) for each of the second-line anti-TB drugs. It is clear from the WHO recommendations that the first choice is to use individualised regimen tailored by DST, the second choice of standardised regimens being determined by the impossibility to perform systematic DST in all MDR/XDR-TB strains. However, with the gradually increasing number of advanced DST laboratories, the individualised regimens are bound, in the future, to replace the standardised regimens in these high burden countries. This in turn may curb the emergence of drug-resistant TB, which mostly results from improper and non-standardised treatment regimens, often prescribed by practitioners in these high burden areas in the absence of DST for individual drugs [4]. The authors recommend early use of linezolid containing individualised regimen on initial detection of second-line drug resistance to achieve better treatment outcomes. However, we would like to mention here that linezolid containing standardised treatment regimen for XDR-TB has already been included in the national treatment guideline of India (one of the sites included in the study) as per the recommendations of WHO, and it does not recommend the use of linezolid in MDR- or pre-XDR-TB [5].

Secondly, nothing has been mentioned about the other drugs included in the treatment regimens. The findings could have been more valid if they were compared with a control group treated with non-linezolid containing regimens. Since linezolid belongs to the group-5 of anti-TB drugs, as per the WHO guidelines, whenever a drug is included from this group it should be accompanied by two or more other drugs from this group [3]. This is particularly important to preserve the efficacy of these relatively newer anti-TB drugs.

While labelled use of linezolid is restricted to 28 days, with dosage of 600 mg twice daily, drug-resistant TB requires a much longer treatment duration, often for ≥ 2 years and, therefore, carries an increased likelihood of severe adverse events, more so if the patient is receiving concurrent antiretroviral therapy [6]. This may lead to drug intolerance and withdrawal of linezolid from the regimen. A recent prospective randomised trial on XDR-TB patients has demonstrated the efficacy of a reduced linezolid dose