New Diagnostics Working Group

Next-generation Whole Genome Sequencing for TB control

A rapid and accurate diagnostic tool for better treatment and prevention

About Tuberculosis

Tuberculosis (TB) is an infectious disease caused by a group of bacilli belonging to the *Mycobacterium tuberculosis* (Mtb) complex. These bacteria usually attack the lungs (pulmonary TB) but can also affect other parts of the body. The classic symptoms of pulmonary TB are a chronic cough, fever, weight loss and night sweats.

TB is transmitted in airborne particles when people who are sick with pulmonary TB expel bacteria by coughing or sneezing. Every day over 4,300 people die from TB and nearly 30,000 people fall ill with this disease. Higher rates of infection are found in low- and middle-income countries.

TB is a preventable and curable disease. It is usually treated with a 6-month course of four antibiotics including rifampicin, one of the strongest medications available for TB treatment. The result is that the patient stops being contagious a short time after starting the treatment. Unfortunately, **there are forms of the disease that do not respond to some of the anti-TB medicines** that are currently available, like rifampicin. These forms of TB can both be transmitted or developed by patients previously affected by TB who have not been treated properly. Curing drug-resistant TB is very expensive. Additionally, the treatment lasts between nine months and two years, and requires the use of medicines that are generally more toxic and involve greater side effects.

Every day	
4,300 people die from TB	**30,000** people fall ill with TB

The WHO's END TB STRATEGY

The World Health Organization (WHO) has developed a strategy to end the TB epidemic by 2030.

One of the key components of this strategy focuses on patient-centered treatment, where each individual with signs and symptoms of TB should undergo early and rapid diagnosis, and if affected by TB, should receive the most appropriate and effective treatment.

The WHO also calls for intensifying research and for the development of new tools and techniques that can optimize TB diagnosis and prevent further dissemination of the disease.

The current approach to diagnosing TB

In many countries the diagnosis of TB still relies on the search for TB bacteria in sputum samples (mucus coughed-up from the trachea and bronchi) using a microscope. However, this methodology lacks sensitivity and so misses many TB cases.

In 2013, the WHO recommended the use of a test called Xpert MTB/RIF for initial TB diagnosis. Xpert MTB/RIF is a rapid and simple test to perform and it simultaneously detects TB and its potential resistance to rifampicin. Gaining information on the resistance profile to one single medicine, such as rifampicin, allows clinicians to identify drug-resistant TB, but is not enough to determine the optimal course of treatment for the patient. The other conventional methods that test for resistance of Mtb to different antibiotics are usually cumbersome and lengthy. This means that many patients affected by drug-resistant TB are not started on appropriate treatment immediately and therefore remain infectious for a longer time and have a higher risk of developing additional resistance.

Advancing TB diagnosis:
Next-generation Whole Genome Sequencing of *Mycobacterium tuberculosis*

Whole Genome Sequencing (WGS) is the process of reading the complete DNA sequence of an organism's genetic material. WGS of Mtb means deciphering the exact sequence of all the nucleotides that form the bacterial genome, thus accessing all the information that it contains. Next-generation WGS (NG-WGS) allows researchers to generate millions of sequences of the genome in a short amount of time. **NG-WGS in TB diagnosis rapidly shows the exact type of Mtb affecting one patient**, including its complete drug resistance profile, and thus allows clinicians to identify the best treatment regimen to combat the disease. The implementation of NG-WGS will benefit the National TB Programmes by providing data for surveillance of Mtb resistance to different anti-TB drugs, an important information for high-burden countries to set TB control strategies and priorities.

Genome

The genome is the genetic material of an organism, its DNA. It carries all the information necessary to create and maintain the organism. The genome of *Mycobacterium tuberculosis* is a sequence of four million letters called nucleotides.
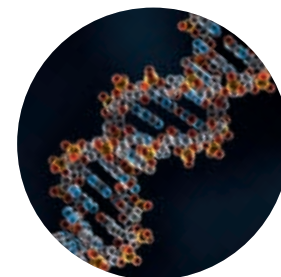
Better treatment for the patient

Next-generation Whole Genome Sequencing enables faster and more accurate diagnosis compared to other TB testing methods. While conventional techniques require months to confirm TB and to identify the most effective medicines for treatment, NG-WGS allows laboratory staff to provide this information in less than two weeks. This means that **patients can be treated with the right medication much more quickly**. Since the right medication is administered from the start, there is also a lower risk of the patient developing resistance to antibiotics. This increases the success of curing patients already affected by drug-resistant TB. Moreover, the delivery of tailored and more effective treatments shortens the time that patients are infectious which **limits the spread of the disease in the community**.

Better prevention for the community

By comparing the genomes of Mtb isolated from different patients it is possible **to infer in a very accurate way where TB transmission has occurred**. In other words, it is possible to understand whether the disease has been caused by the same exact bacteria that spread from one individual to the other.
NG-WGS allows researchers to monitor the dissemination of successful or more virulent bacteria and to track transmission chains within the community. The capacity to rapidly detect TB outbreaks and to define with more accuracy transmission patterns **improves the effectiveness of public health interventions** aimed at controlling and preventing the spread of TB.

Overcoming challenges

Next-generation Whole Genome Sequencing of TB has been used in the research field for more than a decade, but its introduction into clinical practice and routine care is only very recent. The WHO has recognized that NG-WGS has great potential for rapidly diagnosing drug-resistant TB in diverse clinical settings. However, the uptake of this technology particularly in low- and middle-income countries has been hampered by the high costs of the equipment, the requirement for technical training, the need for expert guidance on the clinical interpretation of WGS data, and the lack of simple solutions to obtain genome sequencing information directly from sputum samples. Academia, non-governmental organizations, and international agencies are currently working on several large-scale projects to provide guidelines and to develop tools to facilitate WGS implementation and integration into laboratory workflows. Similarly, industry will need to bring to the market more robust, automated and affordable sequencing platforms in order to unleash the full potential of this technology in endemic countries.

Winning the fight against TB

The use of NG-WGS will transform and accelerate the delivery of personalized treatment to patients affected by TB, thus revolutionizing the way TB is diagnosed and treated. Progress in the development of portable and user-friendly next-generation sequencing instruments coupled with a significant reduction in costs, will make this technology more accessible for diagnostic laboratories in low-and middle-income countries. Future developments of NG-WGS will allow clinicians to test and treat patients at their bedside and to bring the TB and drug-resistant TB epidemic closer to an end.

Stop TB Partnership

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www.stoptb.org